

C O N T E N T S

The American Journal of Medicine

Vol. XVII JULY, 1954 No. 1

Editorial

- Pathogenesis of Hypertension of the Portal Circulation ELI MOSCHCOWITZ 1

Clinical Studies

Clinical and Hemodynamic Studies of Congenital Pulmonic Stenosis with Intact Ventricular Septum

HOWARD A. JOOS, PAUL N. YU, FRANK W. LOVEJOY, JR., ROBERT E. NYE, JR.
AND JOHN H. SIMPSON

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This is a detailed clinical and hemodynamic study of twenty-six patients with congenital pulmonic stenosis (for the most part of the valvular type) with intact ventricular septum, some with patent foramen ovale. It is becoming increasingly apparent that this anomaly is not rare and that it is usually associated for many years with little or no disability. The auscultatory, x-ray and electrocardiographic characteristics, which are described, suggest the diagnosis but confirmation usually depends upon the results of catheterization to establish the altered circulatory dynamics. Despite the paucity of symptoms in many cases, the authors support the view that pulmonary valvulotomy at some favorable period in life is indicated to forestall possible shortening in life expectancy.

Relationship of the Physiologic Third Heart Sound to the Jugular-venous Pulse

E. E. EDDLEMAN, JR., KATHRYN WILLIS, PHETT P. WALKER, LYNN CHRISTIANSON
AND J. RUSH PIERCE

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In recent years the third heart sound often heard in young normal subjects has been considered to occur during the period of maximal ventricular filling. The present study reverts to the older view that it is produced by the opening of the atrioventricular valves, hence is a physiologic opening snap. An exaggerated opening snap consequently is not necessarily indicative of mitral stenosis.

Clinical Studies with the Citrovorum Factor in Megaloblastic Anemia

R. JANET WATSON, HERBERT C. LICHTMAN, JACQUELINE MESSITE, ROSE RUTH
ELLISON, HAROLD CONRAD AND VICTOR GINSBERG

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Citrovorum factor, probably the biologically active form of folic acid, resembles the parent compound in its clinical effects, for example in accelerating development of combined system disease, while causing hematologic remission, in addisonian pernicious anemia. The drug is therefore contraindicated in such cases. The present study indicates, however, that there are, in man, nutri-

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tional megaloblastic anemias (in which free HCl is present in the gastric juice) characterized by a specific deficiency in citrovorum factor. In such cases administration of this drug may be life-saving whereas vitamin B₁₂ is without effect.

Hematologic Studies on Patients with Sickle Cell Anemia Following Multiple Transfusions

CHARLES C. DONEGAN, JR., WILLIAM A. MACILWAINE AND BYRD S. LEAVELL 29

In view of the limited supportive therapy ordinarily given in the management of emergencies associated with sickle cell anemia, this study of the effects of multiple transfusions—tantamount to exchange transfusion—is of unusual interest. Excessive erythropoiesis is depressed, the number of circulating sickled erythrocytes sharply declines, hemolysis decreases, although maximal effects persist usually for only two to three weeks; this may be long enough to carry the patient through some awkward situation such as crisis, surgery or delivery.

Untoward Hematologic Responses to the Antithyroid Compounds

THOMAS HODGE MCGAVACK AND JACQUELINE CHEVALLEY 36

The authors review the recorded experience in respect to bone marrow depression by antithyroid compounds, with special reference to the two most widely employed agents, propylthiouracil and methimazole. Practical pointers on how to minimize such toxic reactions are given.

Hereditary Hemorrhagic Telangiectasia. Nine Cases in One Negro Family, with Special Reference to Hepatic Lesions

J. LAWTON SMITH AND MERRILL I. LINEBACK 41

This report is of interest on several counts, not the least being the stress rightly placed upon nasopharyngoscopic examination for visualization of telangiectasia responsible for recurrent and intractable epistaxes in individuals, particularly infants, who do not have cutaneous manifestations of the disease. The significance of hepatomegaly in this disorder also is discussed rewardingly.

Multiple Myeloma Simulating Aplastic Anemia

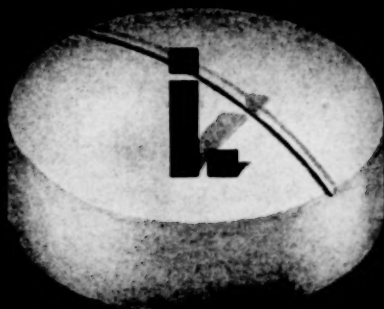
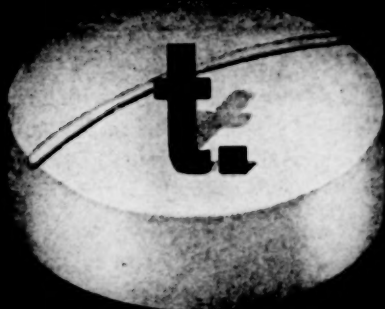
THOMAS N. JAMES AND RAYMOND W. MONTGOMERY 50

The authors call attention to the fact that multiple myeloma may present as aplastic anemia with pancytopenia and cite three cases (of a series of fifty-eight cases of multiple myeloma) in point.

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Evidence is given that the depressant effect on the bone marrow is due not only to replacement of hematopoietic elements but probably also to the action of a humoral suppressive agent.

Review

Hemophilia and Hemophilia-like Diseases Caused by Deficiencies in Plasma Thromboplastic Factors: Anti-hemophilic Globulin (AHG), Plasma Thromboplastin Component (PTC) and Plasma Thromboplastin Antecedent (PTA)

ROBERT L. ROSENTHAL 57

That ancient disease, hemophilia, has recently been discovered not to be an entity but to comprise several distinct defects in plasma thromboplastin factors, each an integral disorder separable on appropriate laboratory study and probably also clinically and genetically. The present study brings together current information regarding three such disorders: hemophilia proper, or anti-hemophilic globulin (AHG) deficiency; plasma thromboplastin component (PTC) deficiency; and plasma thromboplastin antecedent (PTA) deficiency. The distinction is more than academic since management and prognosis vary with each disease.

Seminars on Antihypertensive Drugs

Pharmacology of Antihypertensive Drugs HAROLD D. GREEN 70

The development and appraisal of antihypertensive drugs is still in flux but these agents have already proved to be sufficiently useful to warrant a round robin of informed opinion at this time. Our seminars are introduced by this orientating analysis of principal pharmacologic actions of the most commonly employed categories of antihypertensive drugs, and Dr. Green thus furnishes a firm foundation for interpretation of subsequent descriptions of clinical experience. After a general consideration of the basic mechanisms responsible for increasing blood pressure, and the various ways in which normotension could be maintained, the author proceeds to a systematic description of the pharmacologic effects of the most useful of currently employed antihypertensive agents. Considered are the adrenergic blocking drugs, the ganglionic blocking drugs, the veratrum group capable of reflexly induced lowering of blood pressure, the Rauwolfia depressants and, finally, the hydralazines.

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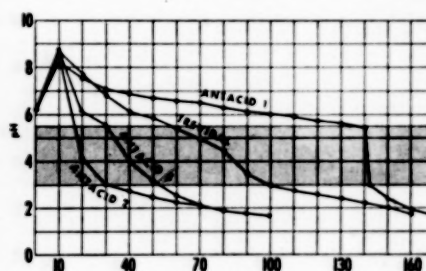
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*Contents continued from page 7**Clinic on Psychosomatic Problems*

- A Case of Arrested Rheumatic Heart Disease with Severe Neurosis Mistaken for "Ulcerative Colitis" 84

Clinic on Psychosomatic Problems (Massachusetts General Hospital)—The case discussed in this Conference presents certain aspects of general medical interest related to prolonged hospitalization for childhood rheumatic fever, and a specific neurosis attributed to excessive masturbation. Bleeding from the rectum was first thought to indicate ulcerative colitis but further examination, including analysis of the psychologic structure, ruled out this diagnosis.

Clinico-pathologic Conference

- Acute Gastrointestinal Bleeding Complicated by Pleural and Pericardial Infection 89

Clinico-pathologic Conference (Washington University School of Medicine)—This case, in view of its very rapid, downhill course and unusual complications, proved to be a very puzzling problem in diagnosis during life, as indicated by the varied opinions expressed in the discussion of the case. Even the necropsy findings leave many questions in interpretation.

Research Society Abstracts

- Western Society for Clinical Research—Abstracts of Papers Presented at the Seventh Annual Meeting, Portland, Oregon, January 29 and 30, 1954 101

Case Reports

- Physiologic Studies in a Patient with a Pulmonary Arteriovenous Fistula
HERBERT N. HULTGREN AND FRANK GERBODE 126

Clinically, pulmonary arteriovenous fistulas may closely simulate cyanotic congenital heart disease or polycythemia vera, for reasons clearly brought out in this paper, but the distinction is important because of the possibility of cure by surgical removal of the fistula. The results of pre- and postoperative studies at rest and after exercise, as described, are of exceptional interest and touch upon many intriguing points.

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- Cushing's Syndrome Produced by a Pituitary Basophil Carcinoma with Hepatic Metastases W. H. SHELDON, A. GOLDEN AND P. K. BONDY 134

The site of the initiating lesion in Cushing's syndrome is still a controversial matter although the consensus now is that the primary lesion usually involves the adrenal cortex. The interesting case here described, however, is one of a few in which the syndrome clearly originated in the adenohypophysis, the site of a primary basophil cell carcinoma.

- Cruveilhier-Baumgarten Syndrome. Review of the Literature and Report of a Case
TSUNG O. CHENG, GEORGE C. SUTTON AND DON C. SUTTON 143

The subject of Cruveilhier-Baumgarten disease and syndrome is of intriguing interest and is set forth here lucidly. A new case is presented, notable for the detailed description of the venous liver hum (which can be very confusing at times) and for application of a glucose absorption test to establish anastomosis of the dilated abdominal wall veins with the portal vein system.

- Pulmonary Fibrosis Due to Chronic Granulomatous Pneumonitis of Unknown Etiology . HOWARD M. DuBOSE, ROBERT S. MEADOR AND BERNICE E. MCCAIN 151

Another necropsy-established example of diffuse interstitial pulmonary fibrosis, possibly related to histoplasmosis, with progressive impairment of ventilation and alveolar-capillary diffusion, and death due to cor pulmonale with failure. Of special interest are the findings of lung biopsy some years before death—this showed chronic granulomatous pneumonitis to have preceded the ultimate development of interstitial fibrosis and emphysema.

- Whipple's Intestinal Lipodystrophy MICHAEL J. LEPORE 160

A biopsy-proven case of Whipple's disease (intestinal lipodystrophy) with good response to corticosteroid therapy, particularly to hydrocortisone in the form of the free alcohol.

Advertising Index on 3rd Cover

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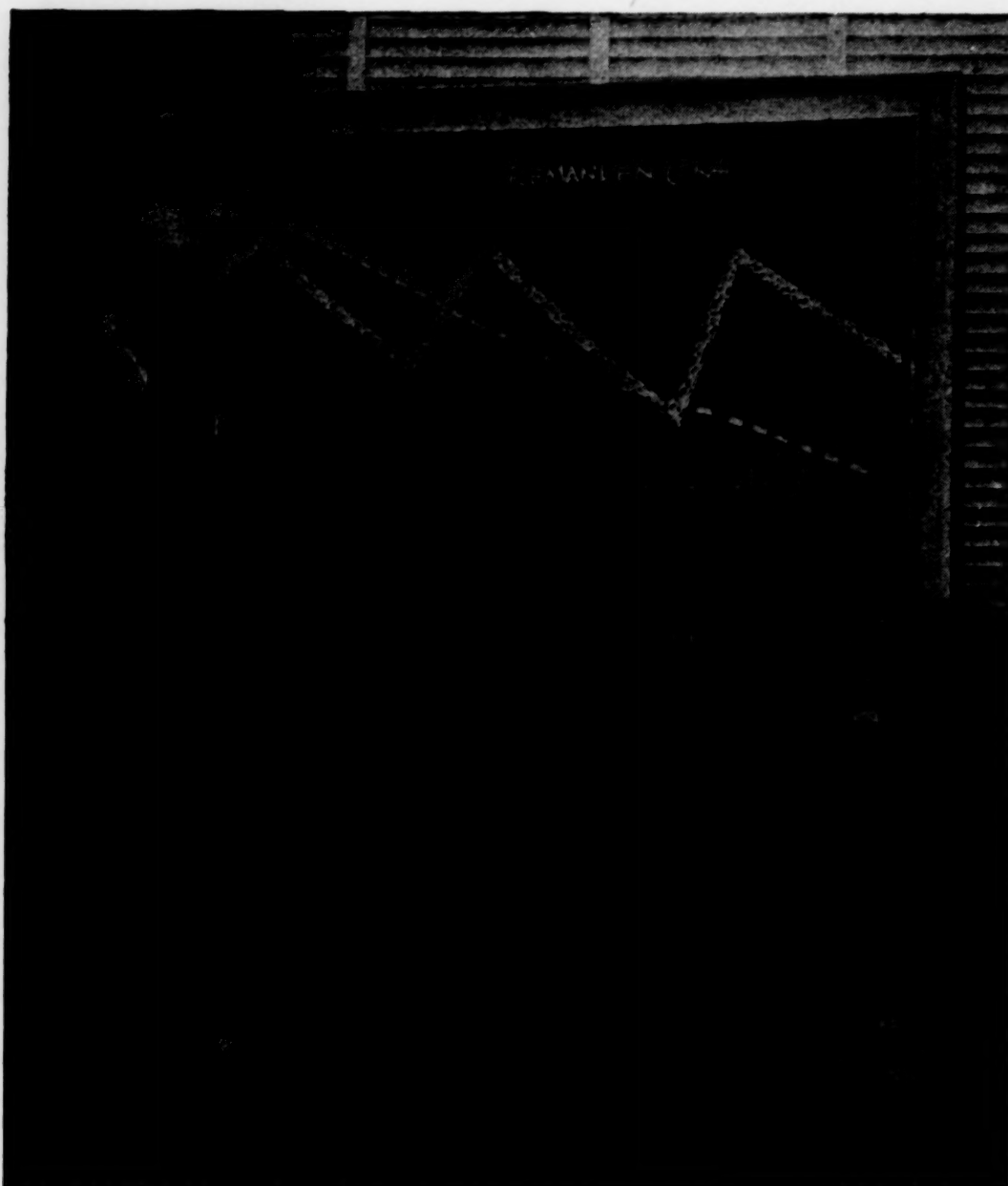
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Reference: 1. Antibiotics & Chemotherapy 2:555, 1952.



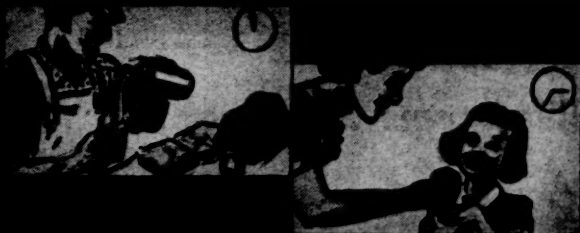
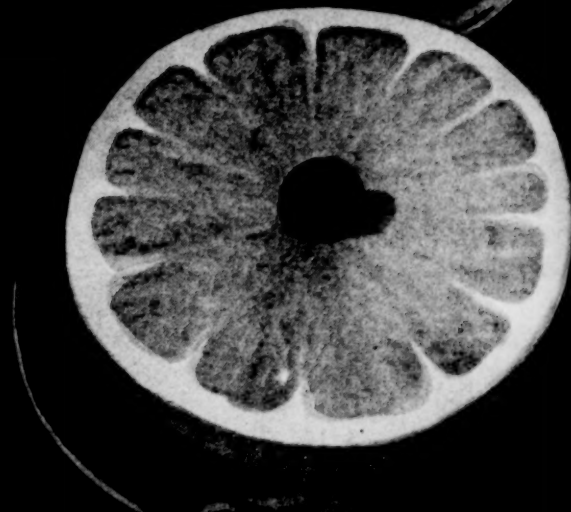
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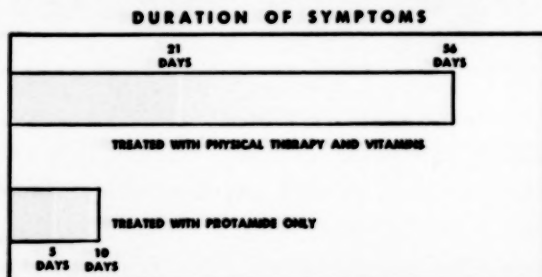
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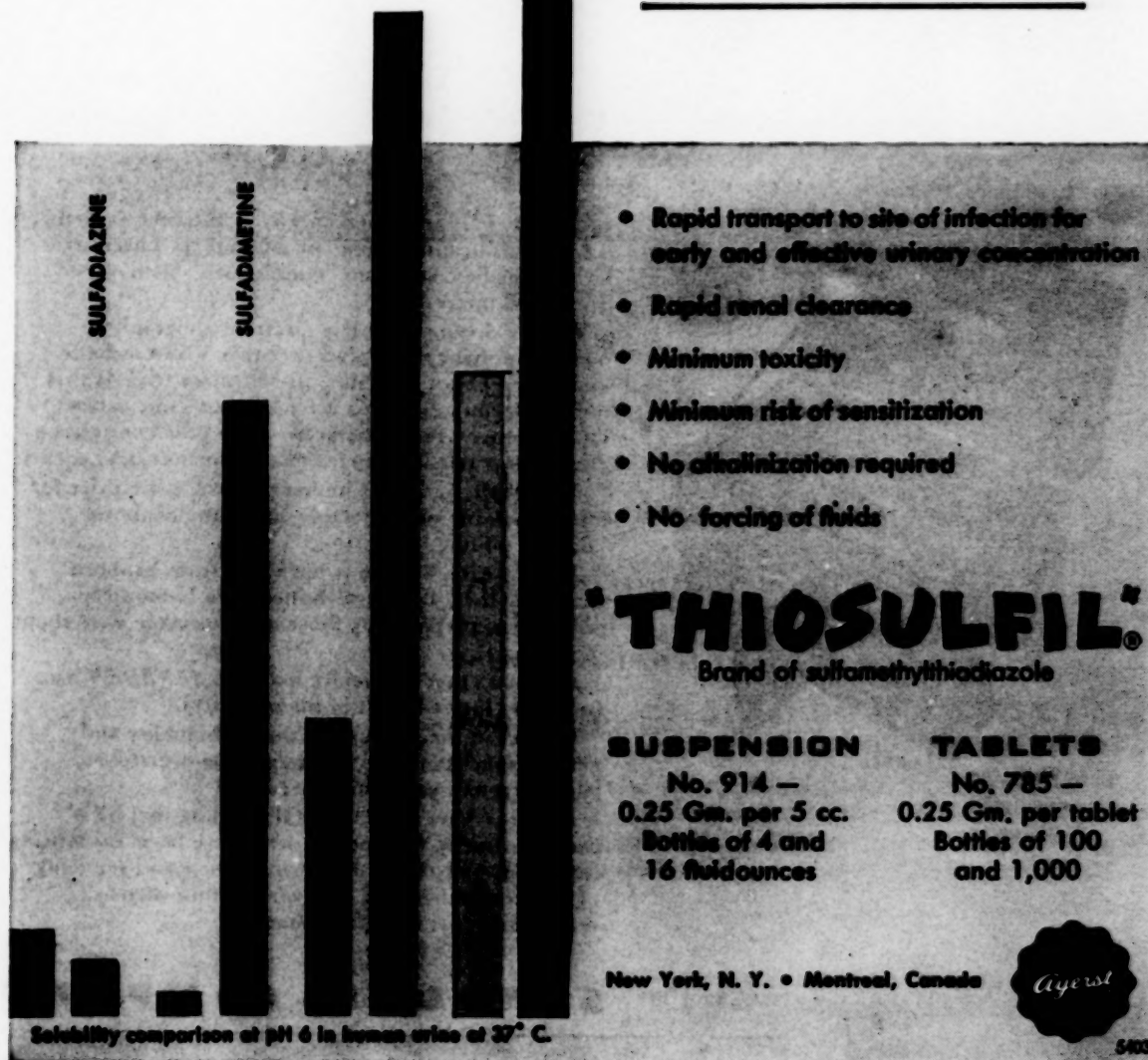
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1. Gourzis, J. T.; Sonnenschein, R. R., and Barden, R.: Alterations in Cardiovascular Responses of the Dog Following Rauwiloid, An Alkaloidal Extract of *Rauwolfia serpentina*, *Proc. Soc. Exper. Biol. & Med.* 85:463 (Mar.) 1954.

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1. Page, I.H.: In Stroud, W.D.: *Diagnosis and Treatment of Cardiovascular Disease*. F. A. Davis Co., Philadelphia, 1952, p. 1033

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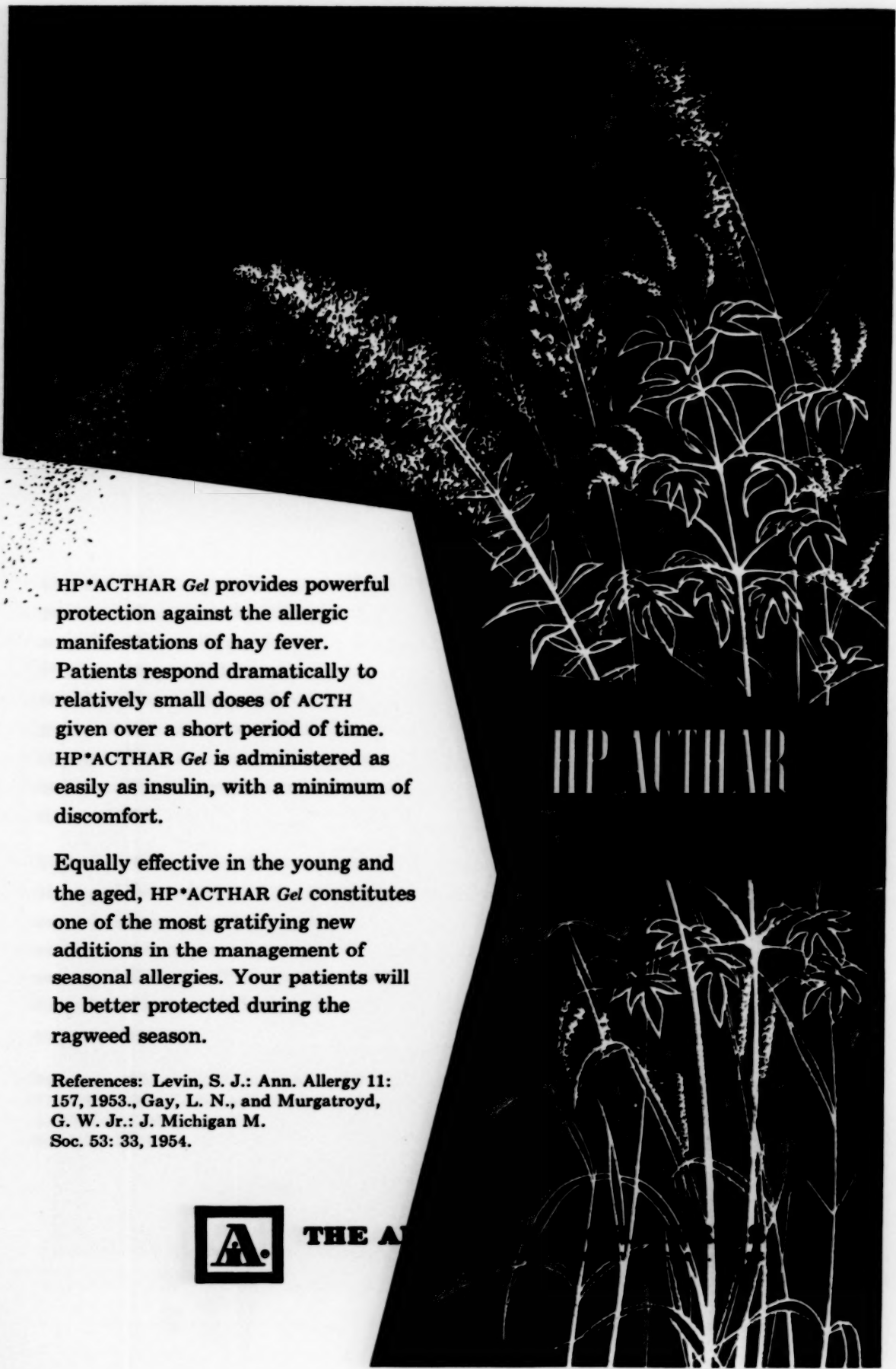
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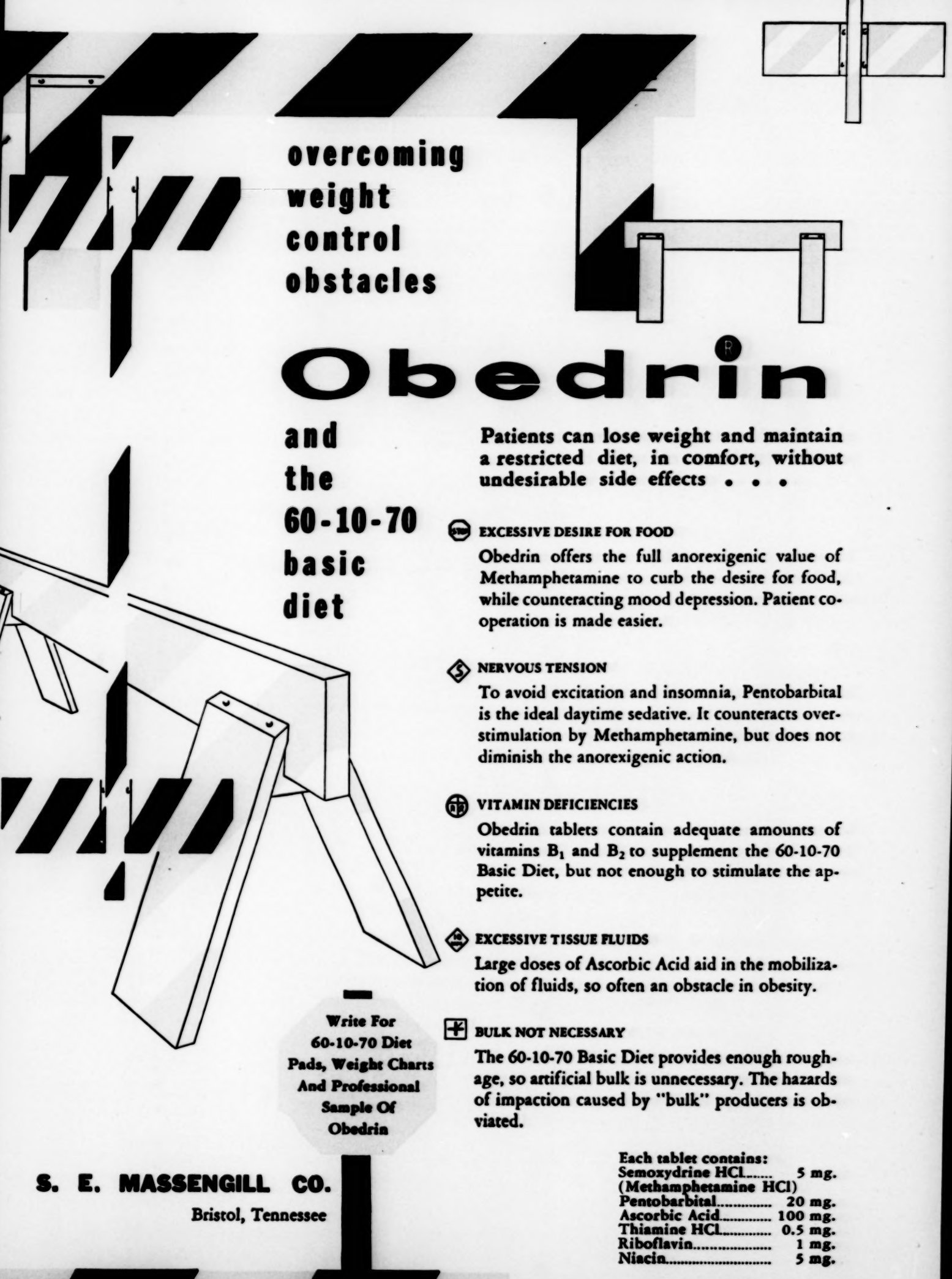
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References: Levin, S. J.: *Ann. Allergy* 11: 157, 1953., Gay, L. N., and Murgatroyd, G. W. Jr.: *J. Michigan M. Soc.* 53: 33, 1954.



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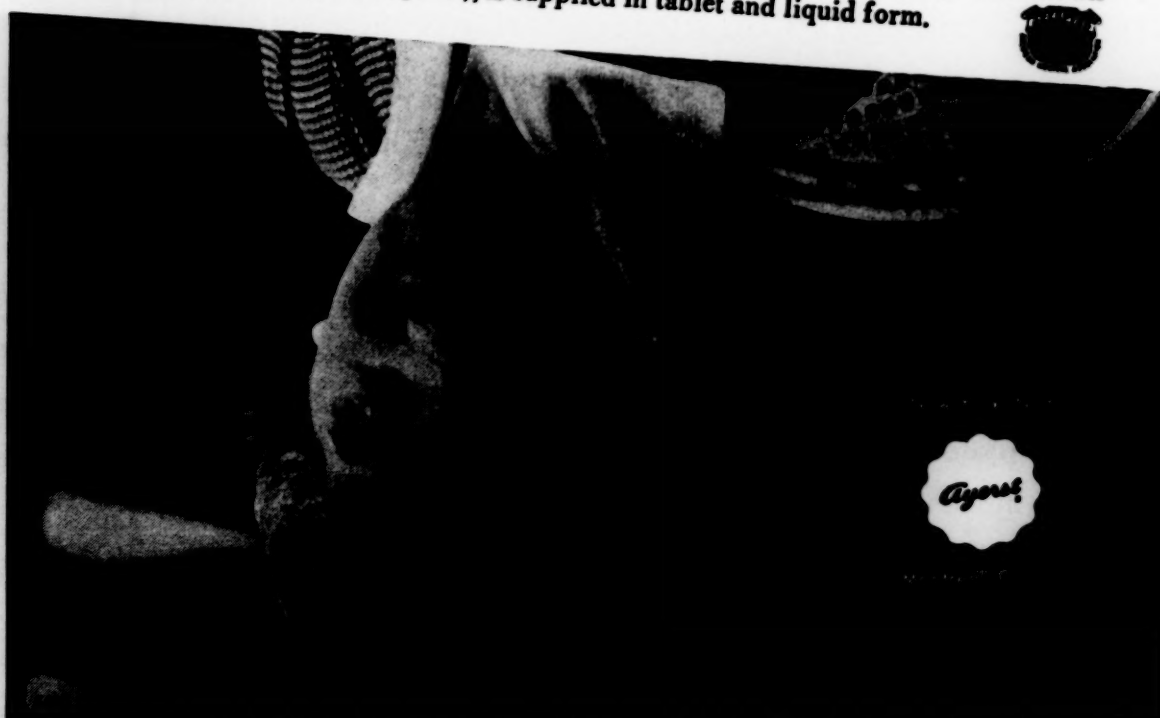
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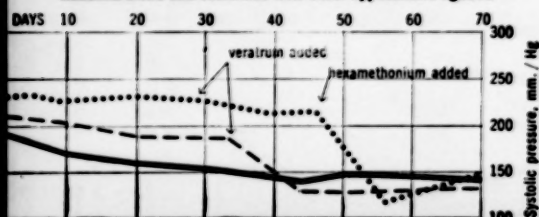




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*Proc. Soc. Exper. Biol. & Med., 80:458, 1952.

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Editorial

Pathogenesis of Hypertension of the Portal Circulation

THE portal circulation differs from the systemic venous system in a number of particulars, among these: (1) It is without valves; (2) it is intercalated between two capillary systems, draining the capillaries of the gastrointestinal tract, gallbladder, pancreas and spleen on the one hand, and emptying into the sinusoidal network of the liver on the other. About 75 per cent of the blood supply of the liver is derived from the portal vein and 25 per cent from the hepatic artery. Inasmuch as the normal pressure in the portal vein is of the order of 8 to 13 mm. of mercury systolic and the normal pressure in the hepatic artery is practically that of the radial artery, averaging 120 mm. mercury systolic, equalization of these pressures within the liver is essential. I have tried to show that this is attained in the following manner:¹ (1) The portal venous capillary network is more extensive than the hepatic arterial network and contributes significantly to lowering the peripheral resistance. (2) It has been shown that the average terminal hepatic arterioles are only 8 microns in diameter while the average of the hepatic sinusoids is 9 microns, so that at the point of communication with the sinusoid there is an abrupt sudden widening. While at first blush this seems a small difference, the difference assumes much greater proportions when one takes into consideration the enormous vascular network. (3) Wakim and Mann² have shown that there are anastomotic communications between the corresponding ramifications of the portal vein and the hepatic artery in their interlobular course. These modes of equalization

of pressures are important because in certain cardiac disorders accompanied by prolonged portal hypertension compensatory mechanisms arise, resulting in new communications between the portal and hepatic vein branches within the liver substance. In this way an intrahepatic Eck fistula is formed. One of the final anatomic results is hepatic cardiac fibrosis which may be interpreted as a venocapillary sclerosis.³ Inasmuch as the splenic vein has no direct anastomotic communication with the systemic venous circulation, portal hypertension causes more severe morbid changes in the spleen than in any of the other organs drained by the portal circulation. These changes are comprised under the indifferent term, "congestive splenomegaly."

"Congestive splenomegaly," as I have tried to show,⁴ is the distinctive anatomic touchstone of portal hypertension, and in order to elucidate the pathogenesis of this lesion it is necessary to give a brief description of the finer anatomy of the splenic circulation. Fortunately, some of the disputed questions concerning the finer anatomy of the spleen have recently been clarified. The splenic artery penetrates the capsule at the hilum and passes into the trabeculae with which it branches, the branches becoming progressively smaller. When the arteries reach a caliber of 40 to 60 μ , they leave the lymphatic tissue and enter the red pulp. Here they branch into straight penicillary vessels which have three successive parts: (1) the artery of the pulp; (2) the Schweigger-Scheidel sheathed portion and (3) the terminal capillaries of the pulp. It

¹ MOSCHCOWITZ, E. The pathogenesis of the hepatic fibrosis associated with hyperthyroidism. *Arch. Int. Med.*, 78: 497, 1946.

² WAKIM, K. G. and MANN, F. C. The intrahepatic circulation of blood. *Anat. Rec.*, 82: 233, 1942.

³ MOSCHCOWITZ, E. The morphology and pathogenesis of cardiac fibrosis of the liver. *Ann. Int. Med.*, 36: 923, 1952.

⁴ MOSCHCOWITZ, E. The pathogenesis of splenomegaly in hypertension of the portal circulation; "congestive splenomegaly." *Medicine*, 27: 187, 1948.

is in the manner of termination of these pulp capillaries into the venous system that controversy has centered, whether the spleen has an open or a closed circulation. The weight of evidence at present is overwhelming in favor of an open circulation. The venous sinuses, unlike the veins, are not lined by flat endothelium but by narrow cells parallel to the long axis of the vessel. The wall of the sinus represents only flattened, cytoplasmic reticulum-containing stomas. It is through these stomas that free blood cells lying within the meshes of the pulp cords flow into the veins. The sinuses unite to form the pulp veins, which enter into the trabecular veins. These in turn unite to form the splenic vein. To return to the terminal capillaries of the pulp, it has been amply demonstrated that these capillaries end in a funnel-shaped dilatation, the ampulla of Thoma, which, like the splenic sinuses is also perforated. The funnel enters directly into the meshes of the pulp reticulum. The interstices of the pulp therefore provide the only system of communication between the artery and the vein. According to Mackenzie and his co-workers,⁵ the pulp spaces in the relaxed spleen measure 6 μ in width but the diameter of the dilated spaces is 16 μ . This potential dilatation, together with that of the sinuses, affords a measure of the distensibility of the normal organ, and accords with the observation of MacMichael who found that the spleen could not be distended to more than three times the normal size.

It is necessary to add that no matter what genetic interpretation and nomenclatures have been suggested for the cells of the splenic pulp, these cells, according to Klemperer,⁶ may differentiate under morbid conditions along four different lines: (1) *Hematic*, as evidenced by extramedullary blood formation; (2) *phagocytic*, either of free blood cells or pigment; (3) *fibroblastic*, with formation of newly formed fibrillar reticulum, histiocytes and collagen; (4) *endothelial proliferation*, with formation of new sinuses. These potentialities are all manifested in "congestive splenomegaly."

It is only in the last decade, thanks to the

labors of Whipple and his co-workers, that hypertension of the portal circulation has been transformed from a concept to a reality, by direct measurements of portal pressures in normal and abnormal states.

Broadly speaking, the causes of hypertension of the portal circulation may be intrahepatic or extrahepatic. The intrahepatic causes of hypertension of the portal circulation include Laennec cirrhosis, biliary cirrhosis, toxic cirrhosis, hemochromatosis, schistosomiasis and *hepar lobatum*. Even before measurements were taken in the splenic vein in the cirrhotoses, a hypertension of the portal circulation was presumed in these conditions because of the frequent association of esophageal varices. Furthermore, "congestive splenomegaly" is practically always present, especially in the late phases. Thompson found unusually high pressures in schistosomiasis because the parasites block the finer nodules of the portal vein within the liver.

Extrahepatic causes of hypertension of the portal circulation include chronic thrombosis of the portal or splenic veins, cavernous transformation of the portal or splenic veins, stenosis of the portal or splenic vein, thrombosis or endophlebitis of the hepatic veins, the Cruveilhier-Baumgarten syndrome, and chronic congestive failure.

Chronic thrombosis of the portal and splenic veins is the commonest extrahepatic cause. The spleen as a rule is larger than in cirrhosis because the portal hypertension is sustained over a more prolonged period. However, thrombosis of the portal and splenic veins is by no means uncommon in portal cirrhosis. Under such circumstances, both the size of the spleen and the histologic findings are intensified. The causes of the thrombosis are various. In many instances no cause can be detected. In others, it may occur following rheumatic fever and after infections such as appendicitis and pancreatitis. A number have been reported following trauma. In The Mount Sinai Hospital we have observed quite a number of cases following thrombocythemia.

Cavernous transformation of the portal or splenic veins should, strictly speaking, be included in the foregoing classification since Klemperer⁷ has brought forward conclusive evidence that it represents the terminal phase of the canalization of a thrombus combined with the formation of

⁵ MACKENZIE, D. W., WHIPPLE, A. O. and WINTERSTEINER, M. P. Studies on the microscopic anatomy and physiology of the living transilluminated spleen. *Am. J. Anat.*, 68: 397, 1941.

⁶ KLEMPERER, P. The Spleen. Chapter in *Handbook of Hematology*, edited by H. Downey. New York, 1938. Paul B. Hoeber and Co.

⁷ KLEMPERER, P. Cavernous transformation of the portal vein. *Arch. Path.*, 6: 353, 1928.

new collateral channels within the lesser omentum. In The Mount Sinai Hospital we have seen eight cases, five of the portal vein and three in the splenic. In three the cause was a thrombocythemia.

Stenosis of the portal or splenic vein. Larrabee has reported three cases of congestive splenomegaly due to adhesions following operation for acute appendicitis. Of the four cases occurring in The Mount Sinai Hospital, three were the result of compression by malignant neoplasms, the fourth was due to a ridge, perhaps congenital, at the junction of the splenic and superior mesenteric veins. Billman and Pohl⁸ have reviewed the subject of congenital stenosis of the portal vein.

Thrombosis or endophlebitis of the hepatic veins. Two of our cases showed an advanced degree of "congestive" splenomegaly, confirming a surmise that obstruction of the hepatic veins gives rise to hypertension of the portal circulation. No evidence of an anastomotic circulation was found in our cases but Thompson and Turnbull reported esophageal varices in two.

We have had no opportunity to examine a spleen from a case of *Cruvelhier-Baumgarten disease* but the circulatory disturbance is such that hypertension of the portal circulation must ensue. Bengue and Eppinger described morphologic changes in the spleen comparable to those of "Banti's disease."

The *cardiac disorder* par excellence which causes hypertension of the portal circulation is constrictive pericardium. There are a number of indirect indications that persistent hypertension of the portal system occurs in constrictive pericarditis. (1) In three of our ten cases the hepatic veins showed pronounced phleboscclerosis, evidence of prolonged elevated venous pressure; (2) I found sclerosis of the portal and splenic vein in some cases of constrictive pericardium; (3) there are fairly marked lesions of "congestive splenomegaly" in most cases.

It therefore seemed pertinent to study the spleen in certain valvular defects of the heart associated with prolonged congestive failure and sustained high peripheral venous pressure, such as advanced mitral stenosis with relative tricuspid insufficiency or organic tricuspid insufficiency or stenosis. We reported fifteen such cases in which the spleen showed the earlier but

unmistakable morphologic changes of "congestive" splenomegaly.⁴ These represented patients who gave stories of repeated and prolonged attacks of congestive failure with very marked and sustained elevation in venous pressure. The "congestive" splenomegaly was somewhat more fibroblastic in those cases with cardiac fibrosis of the liver than in those without, but morphologically they were indistinguishable from the changes found in the earlier phases of extrahepatic obstruction. Added evidence of prolonged hypertension of the portal circulation in such cases is the collagenous and elastic thickening of the intima of the portal vein found upon microscopic examination. Klempner⁶ states that "in prolonged cases of passive congestion the Malpighian bodies may decrease in size. The cytoplasmic reticulum and the free white cells may diminish in number. The reticulum fibres become slightly prominent and the capsule and trabeculae thickened." Smith and Gault⁹ remark that the ultimate phase of chronic passive congestion may be difficult to differentiate from "Banti's disease" or hepatic cirrhosis.

Other influences modify the picture profoundly, the most important being the duration of the obstruction. This is manifest in the marked difference in morphology of the spleen in acute, subacute and chronic vascular obstructions. Undoubtedly, the height of the venous hypertension is a factor since, as Thompson has pointed out, the greater the density and distortion of the fibrosis in portal cirrhosis, the greater the splenomegaly.

I have tried to show in a study of eighty-six cases of congestive failure that the finer morphologic lesions of "congestive splenomegaly" are not the result of congestion but of venous hypertension. Congestion and venous hypertension are obviously not physiologically identical. The term "congestive splenomegaly" is therefore inappropriate.

It must be appreciated that these morphologic changes are not always full-blown but represent a biologic range from the earliest stage to the most mature lesion. Opportunity to study this progressive development arose from observation of many spleens in cases of thrombosis of the portal vein, from the stage of the fresh red thrombus to the full organized form as represented by cavernous transformation. This has

⁸ BILLMAN, F. and POHL, C. Zur Klinik und Pathogenese der Pfortaderstenose in Kindesalter. *Virchows Arch. f. path. Anat.*, 300: 277, 1937.

⁹ SMITH, L. W. and GAULT, E. S. *Essentials of Pathology*. New York, 1940. D. Appleton-Century Co.

been supplemented by the study of simultaneous lesions in a few accessory spleens. In the earliest phase the spleen is enlarged to a size representing extreme distensibility of the organ, three times the normal. The spleen is filled with blood and the sinuses are not visible. The splenic cords are broken up and the pulp cells are widely dispersed. The Malpighian bodies are small due to hemorrhagic infiltration in the periphery. In the next stage, when the thrombus is grey, the sinuses again become visible, are widely dilated and the lining endothelium is flattened. The splenic cords are narrowed and the pulp spaces are distended with erythrocytes. The spleen has shrunk somewhat. In the succeeding stage, when the thrombus has become partially organized, the splenic cords begin to widen, the pulp cells increase and have undergone fibroblastic change and well defined sinuses appear which are dilated and lined by flat endothelium. The Malpighian bodies are small and the hyperemic peripheral zone is now minimal. The spleen is still larger than normal. When the thrombus has become completely fibrous the splenic cords are wide and the pulp spaces contain only a few erythrocytes. The pulp cells become predominantly fibroblasts, the sinuses show extensive hyperplasia and are so prominent that the section appears angiomatous. The walls of the sinuses are thicker, the trabeculae are increased in size, and the edges begin to show "Aufsplitterung." The Malpighian bodies are smaller, due to peripheral encroachment of the fibroblastic transformation of the pulp. The capsule is thickened. A collateral circulation in the form of varicose esophageal veins is frequently present. When the thrombus has attained the stage of cavernous transformation, the maturation of the process is almost complete. The splenic cords become sclerosed and canalized and the pulp spaces contain a minimal number of erythrocytes. The pulp cells are now all fibroblasts, the sinuses are unusually well defined and the lining endothelium is unusually prominent. Their number is excessive. The Malpighian bodies are much smaller and, in addition to perifollicular fibrosis, a fibrosis around the central vein may appear. The trabeculae show a distinct increase and there is marked "Aufsplitterung." In all such cases a collateral circulation is now well established. Such spleens are large, sometimes attaining 1,200 gm. The maximum phase was noted in a case of cavernous transformation of the splenic vein.

The spleen was huge, measuring 24 by 15 by 6 cm. In this organ the splenic cords were completely fibrous and appeared bloodless. In other words, in this spleen the open circulation was converted to one practically closed.

In the advanced phases of "congestive splenomegaly" areas of extramedullary hematopoiesis are fairly common and megakaryocytes are frequently found within some of the sinuses. These are simultaneous reactions and may be viewed as compensatory.

Banti in his original description¹⁰ held that the fibrosis and "fibroadenie" were specific for the disease which he described. Today, Banti's disease is no longer regarded as an entity since it lacks a consistent background clinically and especially in respect to morbid anatomy. Furthermore, the three stages he described, the splenomegalic, the cirrhotic and the ascitic, are fictitious. In no case of extrahepatic portal bed obstruction does the liver become cirrhotic. For these reasons the term "Banti's syndrome" has supplanted the designation "Banti's disease," and it must be emphasized that even this term is only a clinical and not an anatomic expression. In most cases, Banti's syndrome reflects hypertension of the portal circulation.

The frequency of incidence of phlebosclerosis of the portal or splenic veins in portal hypertension still awaits definitive study. Li¹¹ reported an incidence of 77 per cent. In a current but incomplete study we have thus far noted it in 100 per cent, but the number of cases is still too few. Of one fact we have already assured ourselves, namely, that only a microscopic study is diagnostic; in a number of instances we found a distinct intimal collagenous elastic layer in cases in which grossly the lining of the vein appeared normal. It seems remarkable that the frequency of phlebosclerosis of the portal and splenic vein and its morphologic similarity to the sclerosis that occurs in arteries under the stimulus of hypertension was missed as the clue to the possibility that portal hypertension was the mechanism whereby "congestive splenomegaly" was engendered until MacMichael's study.¹² Banti himself described phlebosclerosis of the portal

¹⁰ BANTI, G. La splenomegalia con cirrosi hepatica. *Lo Sperimentale. Sez. biol. fasc.*, 5: 6, 1894.

¹¹ LI, P. Adaptation in veins to increased venous pressure with special reference to the portal system and vena cava. *J. Path. & Bact.*, 50: 121, 1940.

¹² MACMICHAEL, J. The pathology of hepatolienal fibrosis. *J. Path. & Bact.*, 39: 481, 1934.

veins in his early publication but ascribed it to the same hypothetic toxin that caused the splenomegaly. Indeed, a number of students of "Banti's disease" viewed the phlebosclerosis as "primary" and of unknown origin. I tried to show¹³ that this type of phlebosclerosis was always secondary to prolonged and increased venous pressure, no matter which vein was involved. I also tried to show that when a parenchymatous organ is subjected to prolonged vascular hypertension, whether from the supplying artery or due to interference with venous return, the draining capillaries of these vessels revealed progressive sclerosis. The organs studied were the lungs, liver, pancreas and kidney. The term "arteriicapillary sclerosis" was suggested for the processes in the lung, pancreas and kidney, while the term "venocapillary sclerosis" was suggested for the lesions in the liver. If the pulp spaces in the spleen are viewed as the

¹³ MOSCHCOWITZ, E. The association of capillary sclerosis with arteriosclerosis and phlebosclerosis, its pathogenesis and clinical significance. *Ann. Int. Med.*, 30: 1156, 1940.

anatomic analogues of the terminal splenic capillaries, which physiologically they are, "congestive splenomegaly" at least in its later phases, represents, both in its evolution and its morphology, a venocapillary sclerosis, comparable in every detail to that in the liver. The essential difference between the process in the spleen and that in other organs is a physiologic one. In the spleen, when the morphologic change has attained its maximum, the circulation has been converted from an open to a closed one. In such cases the reservoir function of the spleen is practically destroyed. Teleologically, the capillary sclerosis may be viewed in the same light as arteriosclerosis, namely, as a compensatory adaptation to prolonged hypertension. The mechanism is precisely comparable to that observed in the lung in hypertension of the pulmonary circulation.

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Clinical Studies

Clinical and Hemodynamic Studies of Congenital Pulmonic Stenosis with Intact Ventricular Septum*

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ALTHOUGH congenital pulmonic stenosis is best known in association with the tetralogy of Fallot, several recent reviews have emphasized the frequent occurrence of this lesion with intact ventricular septum.¹⁻⁸ Pulmonic stenosis with patency of the foramen ovale or an interatrial septal defect has been differentiated both from the tetralogy of Fallot and from isolated pulmonic stenosis.¹⁻⁹ The clinical and laboratory findings have been well established and differential diagnosis adequately explored. It is the purpose of the present study to report a series of twenty-six proved cases of pulmonic stenosis with intact ventricular septum, emphasizing certain clinical features, with studies of exercise tolerance and data obtained by cardiac catheterization. Nine of these had a definite and two others a possible right to left shunt through a presumed interatrial septal defect or patent foramen ovale.

MATERIAL AND METHOD

During the past four years twenty-six cases of proved pulmonic stenosis with intact ventricular septum have been studied in this laboratory. These patients ranged in age from five to fifty-two years, with an average of fourteen years. There were fourteen men and twelve women in the group. In twenty-three cases the diagnosis of pulmonic stenosis was established by cardiac catheterization, in two cases at autopsy and in one patient by angiocardiology. Angiocardiology demonstrated pulmonic stenosis in

two patients in whom the diagnosis was also established by cardiac catheterization.

Exercise tolerance tests were performed on a treadmill ergometer according to a method previously described.^{10,11} Fluoroscopic examinations, in general, were made on a horizontal table. Electrocardiograms included three standard limb leads, three augmented unipolar limb leads and six unipolar precordial leads (V₁-V₆). Electrocardiograms made during exercise recorded a modified lead CB.¹¹

Cardiac catheterization was carried out according to a modification of the method of Cournand and Ranges,¹² using a single lumen catheter. When feasible, the catheter was wedged into a distal radicle of one of the pulmonary arteries in order to occlude its lumen. The pulmonary "capillary" pressure was recorded by the method of Hellems, Haynes and Dexter,^{13,14} satisfying the criteria of Fowler and associates,¹⁵ and the catheter was then withdrawn to the pulmonary artery. After insertion of a No. 19 needle into a brachial or femoral artery, cardiac output was determined according to the direct Fick principle. Oxygen consumption was measured by a method similar to that described previously.¹⁰ Mixed venous and arterial blood samples were obtained simultaneously as the oxygen consumption was measured. Pressure in the pulmonary artery was recorded and the catheter was slowly withdrawn to the right ventricle while the pressure was recorded continuously. Finally, the catheter was withdrawn to the right atrium and superior

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vena cava. In appropriate cases attempts were made to maneuver the tip of the catheter through any suspected septal defect. Blood samples and pressure records were obtained from each site.

Pressures were recorded by means of a Statham strain gauge connected to a carrier wave amplifier in a multichannel direct writing oscillograph (Sanborn Poly-Viso four-channel recorder). The electrocardiogram and pneumogram were recorded simultaneously. Pressure records were calibrated with a mercury manometer. Systolic and diastolic pressures were measured for at least three respiratory cycles and the average values calculated. Mean pressures were measured by planimetric integration of the pressure tracings during at least two respiratory cycles. The arbitrary zero point of all pressures was 6.5 cm. posterior to the angle of Louis or, in the case of children, in the mid-axillary line with the patient in a recumbent position.

Total pulmonary resistance and pulmonary arteriolar resistance were calculated according to the formulas of Gorlin and associates.¹⁶ Pulmonary artery flow, systemic flow, right to left shunt, effective pulmonary flow and per cent of mixed venous blood reaching the lungs were calculated by the formulas of Bing and co-workers.¹⁷ Pulmonary valve area and the area of auricular septal defect were determined by the methods of Gorlin and Gorlin.¹⁸ Resistance across the pulmonic valve was calculated by the formula suggested by Dow and associates.⁴ Left ventricular work was calculated by the formula of Gorlin *et al.*¹⁶ The corresponding formula for right ventricular work was modified as follows in order to include work against resistance offered by the obstruction to right ventricular outflow:

$$Wr = \frac{(PAF \times 1.055) \times (RV_{sm} - RA_m) \times 13.6}{1000}$$

where Wr = work of the right ventricle in kg.M/minute/ M^2

PAF = pulmonary artery flow in L./minute/ M^2

RV_{sm} = right ventricular mean systolic ejection pressure in mm. Hg

RA_m = right auricle mean pressure in mm. Hg

1.055 = specific gravity of blood

13.6 = specific gravity of mercury

JULY, 1954

RESULTS

Table 1 summarizes the clinical and laboratory observations in all twenty-six patients.

Clinical. Fifteen of the twenty-six patients were without symptoms referable to the cardiac lesion. Nine patients experienced questionable limitation of physical activity, one of whom described definite dyspnea as an isolated symptom. Two were significantly disabled, one of whom exhibited congestive heart failure and both of whom had a right to left shunt. The second heart sound in the pulmonic area was normal in ten instances, diminished or absent in eleven cases and of unknown intensity in fifteen cases. A systolic murmur was heard in all cases and was maximal to the left of the sternum in the second and third interspaces in twenty-two cases. In two instances the murmur was maximal in the third and fourth interspaces, in one case in the fourth and fifth interspaces, in one case at the apex. With one exception, pulmonic stenosis associated with a systolic murmur maximal below the pulmonic area was suspected to be either infundibular or combined infundibular and valvular as shown by pressure patterns during cardiac catheterization. The intensity of the murmur was not related to right ventricular hypertension or to the gradient of systolic pressure across the pulmonic valve. Fifteen patients had a palpable thrill associated with the murmur. Cyanosis was pronounced in two patients, who also showed clubbed extremities and one of whom had polycythemia.

Horizontal fluoroscopy revealed enlargement of the pulmonary artery segment in twenty cases. The conus segment appeared normal in five patients only one of whom had a significant right to left shunt, and was concave in one. The right ventricle appeared enlarged in fifteen cases and was normal in eleven. Right ventricular enlargement was not closely related to the degree of right ventricular hypertension. The left ventricle was normal in fourteen cases and appeared somewhat enlarged in twelve. Atrial enlargement was noted in four cases in one of whom right to left shunt was definitely absent. Hilar pulsations were absent in twenty-two cases, equivocal in two instances and present in two with coincident patency of the ductus arteriosus. Pulmonary vascular markings were normal or diminished in twenty-four cases and somewhat exaggerated in the two with patent ductus.

Resting electrocardiograms in twenty-five patients showed right axis deviation in fifteen cases, no axis shift in nine and left axis deviation in one. The unipolar precordial leads of sixteen patients showed right ventricular hypertrophy, three showed left ventricular hypertrophy and

which was right to left shunt clearly absent. Occasional premature atrial contractions were recorded in one patient.

Exercise Tolerance. The exercise tolerance of ten patients was studied on the treadmill ergometer. The physical fitness index¹⁹ of five

TABLE I
SUMMARY OF CLINICAL AND LABORATORY DATA IN TWENTY-SIX CASES OF CONGENITAL PULMONIC STENOSIS WITH INTACT VENTRICULAR SEPTUM

	Clinical										X-ray				Electro-cardiogram			Site of Stenosis										
	No Symptoms	Questionable Limitation of Activity	Significant Disability	Normal Second Pulmonic Sound (P ₂)	Diminished or Absent P ₂	Pulmonic Systolic Murmur	Subpulmonic Systolic Murmur	Cyanosis	Clubbing	Polycythemia	Enlarged Pulmonary Artery Segment	Normal Pulmonary Artery Segment	Absent Pulmonary Artery Segment	Enlarged Right Ventricle	Enlarged Left Ventricle	Enlarged Atrium	Right Axis Deviation	Right Ventricular Hypertrophy	Left Ventricular Hypertrophy	Enlarged P Waves	1° A-V Block	Valvular	Probably Valvular	Infundibular	Probably Infundibular	Combined Valvular and Infundibular	Valvular with Possible Combined Infundibular	Unknown
Isolated pulmonic stenosis (13 cases) . . .	10	3	0	5	6	11	2	0	0	0	9	3	1	6	8	1	6	7	1	1	0	5	1	1	1	3	0	2
Pulmonary stenosis, probably isolated (2 cases)	0	2	0	1	1	2	0	0	0	0	2	0	0	2	0	0	2	2	0	0	1	0	1	0	0	0	0	1
Pulmonary stenosis, with atrial septal defect (9 cases)	4	3	2	4	3	9	0	2	2	1	8	1	0	6	3	3	6	6	1	0	2	4	2	0	1	0	1	1
Pulmonary stenosis, with possible atrial septal defect or patent foramen ovale (2 cases)	1	1	0	0	1	0	2	1*	0	0	1	1	0	1	1	0	1	1	1	1	0	0	0	0	0	1	1	0

* Questionable cyanosis.

one suggested combined ventricular hypertrophy. The pattern of left ventricular hypertrophy is unexplained, occurring in cases of proved pulmonic stenosis without clinical or hemodynamic findings suggesting circulatory disease on the systemic side. Fluoroscopic examination showed definite or suspected left ventricular enlargement in the four cases with patterns of left ventricular hypertrophy. One patient had a right bundle branch block and suspected Wolff-Parkinson-White syndrome. Three cases had broad and tall P waves indicating atrial hypertrophy, only one of which had a definite right to left shunt. First degree A-V block occurred in three cases, in only one of

of these was within normal range. Five patients had a physical fitness index of less than 13.3, the lower limit of normal. All five patients with a subnormal physical fitness index were able to walk for the prescribed ten-minute period. One complained of slight fatigue, two noted slight tiring of the legs, two had no symptoms and none noted subjective dyspnea. Four hyperventilated during exercise, the ventilatory rate being more than 12 L./minute/M², STPD. All five exhibited tachycardia during exercise and the first three minutes of recovery. Hyperventilation during exercise accompanied a low respiratory efficiency in two cases. One case (R. L.) of isolated pulmonic stenosis showed a paradoxical

TABLE II
RESTING HEMODYNAMIC OBSERVATIONS IN TWENTY-FOUR CASES OF PULMONIC STENOSIS

Patient	Age	Symptoms	Cyanosis	Right Ventricular Hypertrophy (ECG)	Pulmonary "Capillary" Pressure (mm. Hg)	Pulmonary Artery Pressure (mm. Hg) Systolic/Diastolic, Mean	Mean Right Atrial Pressure (mm. Hg)	Right Ventricular Systolic Pressure (mm. Hg)	Cardiac Index (L./minute/M ²)	Cardiac Output (L./minute)	Pulmonary Artery Flow (L./minute)	Systemic Flow (L./minute)	Arterial Oxygen Saturation (%)	Per cent of Total Mixed Venous Blood Reaching the Lungs	Total Pulmonary Resistance (dynes-sec.-cm. ⁻⁵)	Arterial Pulmonary Resistance (dynes-sec.-cm. ⁻⁵)	Cross Sectional Area of Flow, Pulmonic Valve (cm. ²)	Resistance Across Pulmonic Valve (dynes-sec.-cm. ⁻⁵)	Cross Sectional Area Atrial Septal Defect (cm. ²)	Right Ventricular Work (kg. M/minute/M ²)	Left Ventricular Work (kg. M/minute/M ²)	Pulmonic Stenosis	Poststenotic Dilatation	Interatrial Septal Defect or Patent Foramen Ovale
T. B.	17	±	+	+	10	26/8, 14	10	134	3.1	5.6	5.2	6.4	93	92	198	60	2.0	85	0.6	2.8	2.8	+	+	+
R. S.	15	±	0	LVH	1	20/20, 17	1	32	3.8	6.2	5.8	6.6	93	93	218	78	2.0	85	0	5.0	5.0	+	+	+
V. R.	13	0	0	0	4	19/7, 13	4	44	3.8	5.5	5.5	4.5	95	100	191	125	2.0	85	0	84	84	0	0	0
P. S.	12	0	0	LVH	4	26/15, 17	4	42	5.1	7.0	5.9	6.6	93	86	303	125	2.0	85	0	6.0	6.0	+	+	+
I. R.	8	0	0	CVH	6	23/19, 21	6	65	97	100	+	+	+
T. R.	5	0	0	0	65	95	100	0	0	0
J. M.	52	±	0	0	72	4.1	8.8	8.8	8.5	96	100	147	...	200	0	+	+	+
K. D.	7	0	0	0	6	20/14, 16	6	47	87	72	2.0	200	0	+	+	+
R. W.	7	0	0	+	0	33/8, 23	0	102	6.3	5.2	5.2	4.9	96	100	341	285	0.5	982	0	6.1	7.5	Prob.	Prob.	+
R. G.	26	±	+	+	106	2.7	4.7	4.3	...	94	100	84	0	+	+	+
G. D.	20	±	+	+	116	...	ca. 4.8	77	100	+	+	+
V. H.	18	0	0	+	10	...	10	44	4.9	8.3	5.6	10.4	88	63	223	66	ca. 3.0	+	+	+
M. H.	10	0	0	+	8	...	8	95	90	84	+	+	+
K. S.	5	0	0	+	21	32/24,	7	50	98	0	Prob.	Prob.	+
D. B.	30	D*	+	+	...	30/6, 17	8	94	2.8	5.0	3.6	5.3	84	83	268	+	+	+
K. W.	5	+	+	+	...	20/11, 16	7	57	95	100	207	81	1.0	267	0	1.9	6.5	+	+	+
J. S.	12	0	0	+	9	26/10, 15	4	62	4.4	5.7	5.7	5.6	91	100	+	+	+
L. B.	5	+	+	+	7	32/5, 7	7	73	91	100	+	+	+
M. J. H.	7	0	0	+	...	14/1,	88	97	100	+	+	+
J. B.	6	0	0	+	11	14/7, 14	...	2	114	96	100	+	+	+
W. F.	16	0	0	+	6	25/5, 9	4	86	3.5	5.3	5.3	4.9	97	100	135	45	0.4	688	0	2.5	3.3	+	+	+
N. G.	9	0	0	LVH	7	17/7, 11	-4	28	...	5.1	5.2	5.2	94	100	176	64	0	+	+	+
N. B.	10	±	0	+	5	19/10, 15	3	35	3.3	3.2	2.6	2.3	90	72	379	253	+	+	+
L. S.	18	±	0	0	13	20/10, 15	6	31	4.6	6.8	6.8	5.2	95	100	176	24	1.7	93	0	2.1	5.8	+	+	+

* PFO, patent foramen ovale; D, some dyspnea only.

respiratory response during late exercise (i.e., oxygen consumption per liter of ventilation was lower than the resting value) and a physical fitness index of 8.6. Paradoxical respiratory efficiency during exercise was exhibited by another patient (G. D.) with a large interatrial septal defect, pronounced cyanosis and polycythemia.

Eight of eleven cases with exercise electrocardiograms showed shortening of the Q-T interval corrected for heart rate (Q-T_c) during and immediately following exercise, the response typical of congenital heart disease.¹¹ The Q-T_c interval responded normally in three patients.

Hemodynamic Studies. Table II summarizes pertinent hemodynamic data in twenty-four cases. Pulmonary "capillary" pressure was measured in twelve cases and was normal in all but one. In this case the patient was crying as the record was made and the mean pulmonary "capillary" pressure measured 21 mm. Hg.

Pulmonary artery systolic pressure was measured in eighteen cases and ranged from 14 to 33 mm. Hg. The mean pulmonary artery pressure of twenty-one cases ranged from 5 to 23 mm. Hg with an average of 14.7 mm. Hg. Mean pulmonary artery pressures was less than 10 mm. Hg in only two cases and exceeded 20 mm. Hg in two instances. Thus, despite pulmonic stenosis, mean pulmonary artery pressure was usually maintained at normal levels. Normal pulmonary "capillary" and pulmonary artery pressure have been reported by other authors.^{1,4,7}

Right ventricular systolic pressure varied from 31 to 134 mm. Hg. Thirteen of fifteen patients with electrocardiographic evidence of right ventricular hypertrophy whose right ventricular pressure was measured had a right ventricular systolic pressure of 50 mm. Hg or more. (Table III.) In eleven cases with right ventricular hypertrophy nine had right ventricular systolic pressure greater than pulmonary artery systolic pressure by more than 35 mm. Hg. Among seven cases without electrocardiographic evidence of right ventricular hypertrophy, the right ventricular systolic pressure exceeded 50 mm. Hg in only one case (Table III) and the difference between right ventricular systolic and pulmonary artery systolic pressure in six cases did not exceed 30 mm. Hg. The three patients of Dow and associates⁴ without right ventricular hypertrophy showed similar relationships.

Pulmonary artery flow varied from 2.6 to 8.8 L./minute in fourteen cases with an average

of 5.4 L./minute. Pulmonary artery flow was not statistically related to right ventricular hypertension, right ventricular hypertrophy or exercise tolerance. Systemic flow, ranging from 2.3 to 10.4 with an average of 5.9 L./minute, exceeded pulmonary artery flow in cases with

TABLE III
RELATIONSHIPS OF RIGHT VENTRICULAR AND PULMONARY ARTERY PRESSURE TO ELECTROCARDIOGRAPHIC EVIDENCE OF RIGHT VENTRICULAR HYPERTROPHY*

PA _s	PA _m	RV _s	Δ Systolic
<i>Cases with Right Ventricular Hypertrophy</i>			
26	14	134	108
*†	16	65	...
33	23	102	69
...	5	106	...
...	16	44	...
...	11	95	...
32	..	50	18
30	17	94	64
32	17	73	41
14	..	88	74
14	14	114	100
25	9	86	61
19	15	35	16
20	16	57	37
26	15	62	36
<i>Cases without Right Ventricular Hypertrophy (including those with left ventricular hypertrophy)</i>			
20‡	17	32	11
19	13	44	25
26‡	17	42	16
...	16	72	...
20	16	47	27
17	11	28	11
20	15	31	11

* PA_s, pulmonary artery systolic pressure, mm. Hg; RV_s, right ventricle systolic pressure, mm. Hg; PA_m, pulmonary artery, mean pressure, mm. Hg; Δ systolic, difference between right ventricular and pulmonary artery systolic pressure, mm. Hg.

† Case with suspected ventricular hypertrophy.

‡ Case with left ventricular hypertrophy.

right to left shunt, demonstrated or suspected in eleven cases and varying from 0.8 to 4.8 L./minute in the six cases in whom the size of the shunt could be calculated. In two cases the calculated shunt was too small to be definitely significant.

Among nine cases with right to left shunt, excluding the two doubtful cases, the percentage of total mixed venous blood reaching the lungs

varied from 47 to 85. Neither the volume of right to left shunt nor the per cent of mixed venous blood reaching the lungs correlated with right ventricular systolic pressure or with the gradient between right ventricular systolic and pulmonary artery systolic pressure.

Total pulmonary resistance varied from 84 to 379 (average 218) dynes-sec.-cm.⁻⁵ in fourteen patients, exceeding the maximum normal value of 250 dynes-sec.-cm.⁻⁵ in four instances. In ten of these patients pulmonary arteriolar resistance varied from 24 to 285 dynes-sec.-cm.⁻⁵ exceeding 100 in three. A larger series will be required before variations in pulmonary resistance can be evaluated. Dow and co-workers⁴ found normal pulmonary vascular resistance in all seven of their cases.

The area of the pulmonic valve was calculated in six cases.* The valve areas are in gross inverse relation to the magnitude of right ventricular hypertension. The three largest areas were not accompanied by electrocardiographic evidence of right ventricular hypertrophy. The inverse relation of pulmonic valve area and resistance across the stenotic valve is obvious in Table IV.

An interatrial septal defect was postulated in nine cases as the site of right to left shunt. In one of these a subsequent sample of arterial blood was 97 per cent saturated with oxygen, suggesting intermittent patency of the foramen ovale. The area of the interatrial septal defect was 0.6 and 3.0 cm.² in the two cases from whom sufficient data were obtained to permit the calculation.

Table IV summarizes the relationships of pulmonic valve area, pulmonic valve resistance and right ventricular work. The left ventricular work per minute was 5.0 and 6.0 kg.M/M² (normal 3.7 to 6.9 kg.M/M²) in two of the cases showing left ventricular hypertrophy. One patient with right ventricular hypertrophy and a right ventricular systolic pressure of 134 mm. Hg had a value for left ventricular work per minute of 2.8 kg.M/M². The patient whose right ventricular work per minute was 6.1 kg.M/M² had a value for left ventricular work per minute of 7.5 kg.M/M². His electrocardiogram showed only right ventricular hypertrophy.

The oxygen saturation of arterial blood varied with the pressure and degree of right to left

shunt. The lowest value in nineteen cases was 77 per cent. Eight cases had values less than 92 per cent.

Valvular pulmonic stenosis was proved at postmortem examination in two cases. Pressure patterns recorded during withdrawal of the

TABLE IV
RELATIONSHIP OF PULMONARY VALVE AREA TO RESISTANCE
ACROSS THE STENOTIC VALVE AND TO RIGHT
VENTRICULAR WORK

Cross Sectional Area of Flow, Pulmonic Valve (cm. ²)	Resistance Across Stenotic Pul- monic Valve (dynes-sec.-cm. ⁻⁵)	Right Ventricular Work per Minute (kg.M/M ²)
2.0	85	0.8
2.0	200	...
1.7	93	2.1
1.0	267	1.9
0.5	982	6.1
0.4	688	2.5

cardiac catheter from pulmonary artery to right ventricle yielded a pattern suggesting valvular stenosis in eleven additional cases, in four of which a zone of intermediate pressure suggesting infundibular involvement co-existed. Valvular stenosis was considered probable in four others. In two cases showing the pressure pattern associated with valvular stenosis co-existing infundibular stenosis could be neither established nor excluded. The type of pulmonic stenosis was not demonstrated in four cases. (Table I.) The apparent site of stenosis was not related to the presence of right to left shunt. Poststenotic dilatation of the pulmonary artery was demonstrated by roentgenologic examination in twenty cases. Six cases had no evidence of poststenotic dilatation of the pulmonary artery. In this series the type of pulmonic stenosis suggested by the pressure patterns encountered was not clearly related to the occurrence of poststenotic dilatation.

COMMENTS

Engle and Taussig have written a lucid account of the pathologic physiology of pulmonic stenosis with intact interventricular septum.⁵ Obstruction to right ventricular outflow leads to hypertrophy of the right ventricle and to increasing right ventricular pressure. If the ventricle decompensates, it empties incompletely and the end-diastolic pressure and, in turn, the

* In six additional cases with otherwise adequate hemodynamic data the measurement of right ventricular mean systolic ejection pressure was prevented by inadequate definition of the pulmonary artery pressure cycle.

right atrial pressure rise. When the latter exceeds the left atrial pressure, right to left shunting of blood may occur through an incompletely sealed foramen ovale or through an interatrial septal defect. Cyanosis of increasing severity may result, ultimately causing compensatory polycythemia. Johnson and Johnson⁸ emphasize that the right atrium dilates with increasing pressure and may spread open an unsealed foramen ovale. These authors believe that patency of the foramen ovale in these cases may not represent a true congenital malformation inasmuch as the foramen ovale is probe-patent in 25 per cent of adult hearts examined at autopsy. Engle and Taussig⁵ point out that an affected infant with a relatively adequate pulmonic orifice may outgrow the opening as his size and activity increase, emphasizing the hazard of the lesion during the period of most rapid growth.

The cases in the present series are mostly mild by clinical observation as well as physiologic investigation. Excepting the severest cases, symptoms were few and caused little disability. Two patients without symptoms had a right ventricular systolic pressure exceeding 100 mm. Hg. In two others symptoms were equivocal. The paucity of symptoms in the present series may reflect the mild nature of most of the cases. However, the importance of investigating mild cases is indicated by the frequent findings of right ventricular hypertension and right ventricular hypertrophy in this group. Other authors have commented on the inconspicuous nature of the symptoms often noted^{6,7} and on the failure of frequency of symptoms to correlate with the degree of right ventricular hypertension.^{4,7}

In general, the intensity of the systolic murmur was not closely related to the degree of pulmonic stenosis. This agrees with the findings of Johnson and Johnson⁸ although Dow and co-workers⁴ and Currens and associates²⁰ believed that the intensity of the murmur correlated with the degree of stenosis. Our findings suggest that a murmur heard maximally in the second left interspace is more likely to be associated with a valvular type of stenosis. However, Guinsbourg²¹ was unable to differentiate the type of stenosis by the location of the murmur.

Our roentgenologic studies confirm the classic findings reviewed by Dow *et al.*,⁴ namely, prominent right ventricle and atrium, prominent pulmonary artery and normal or decreased vascular markings. Apparent left ventricular enlargement in twelve cases may be related to

the recumbent position of the patients during examination and, in certain cases, to posterior displacement by an enlarged right ventricle. Thus confirmatory electrocardiographic evidence of left ventricular hypertrophy was obtained in only three instances and combined ventricular hypertrophy occurred in a fourth. These findings have not been previously reported and are unexplained in the present patients.

The characteristic electrocardiographic findings of right axis deviation and right ventricular hypertrophy occurred in the majority of our cases. Persistent incomplete right bundle branch block was encountered in only one case, in whom a short P-R interval (0.08 sec.) aroused suspicion of Wolff-Parkinson-White syndrome. Dow and co-workers,⁴ on the other hand, detected bundle branch block in five of eight cases. Broad, tall P waves suggesting atrial hypertrophy in three of our cases have been described by several authors.^{1,2,5,6,8} First degree A-V block in five of our cases is mentioned by other workers^{1,8} as an associated finding.

The exercise tolerance of the ten patients studied was unrelated to the degree of pulmonic stenosis. Physical fitness index did not correlate with right ventricular hypertension or with the gradient from right ventricular systolic to pulmonary artery systolic pressure. The subnormal physical fitness index of five patients was caused by hyperventilation during exercise and by a rapid heart rate during the first three minutes of the recovery period. All five suffered disproportionate tachycardia during exercise and two showed only a small increase in respiratory efficiency. These responses suggest that cardiac output during exercise was increased largely by increasing the heart rate and that ability to increase the stroke volume may be limited by the narrowed pulmonic orifice. However, Dow and co-workers⁴ found an adequate increase in cardiac output during mild or moderate exercise associated with a sharp rise in right ventricular systolic pressure. Our patients exercised more severely and may have exceeded their ability to increase stroke volume proportionately at higher levels of cardiac output, although measurements of cardiac output during more strenuous exercise will be required for confirmation. Only two of our patients, one of whom had a large right to left shunt, had a paradoxical response to exercise with a fall in oxygen consumption per liter of ventilation. This may indicate that most of the patients were

able to increase pulmonary blood flow during exercise.

Significant physical disability was most frequent in the group of patients with right to left shunt. Poststenotic dilatation of the pulmonary artery and atrial enlargement occurred more uniformly among patients with right to left shunt. In other aspects isolated pulmonic stenosis was similar to these cases.

Almost uniformly, patients showing electrocardiographic evidence of right ventricular hypertrophy had a right ventricular systolic pressure of 50 mm. Hg or more, with the latter usually exceeding the pulmonary artery systolic pressure by more than 30 mm. Hg. The cases of Dow and co-workers⁴ show the same relationships if two patients (T. M. and W. P.) with right bundle branch block and low right ventricular systolic pressure are excluded.

Cardiac index did not correlate with right ventricular hypertension or with right ventricular hypertrophy. This suggests that the relatively mild degree of pulmonic stenosis in most of the present patients did not interfere measurably with cardiac output at rest and is consistent with the results of the exercise studies discussed previously.

The calculated area of the pulmonic valve falls within the range of pulmonic stenosis as indicated by the measurements of Gorlin and Gorlin.¹⁸ The inverse relation of pulmonic valve area to right ventricular hypertension indicates that the latter may provide a gross estimate of the degree of pulmonic stenosis. The calculation of resistance across the stenotic orifice provides a more accurate measure of the burden against which the right ventricle must work. By adapting the formula for right ventricular work¹⁶ to include this factor the added load upon the right ventricle can be readily appreciated.

It has become clear that congenital pulmonic stenosis may often present a mild clinical picture, particularly in childhood. Physiologic studies, however, have established that significant cardiac stress is demonstrable even in patients with little or no physical disability. In addition, many mild cases advance in severity with increasing age. The life expectancy of any patient with congenital pulmonic stenosis seems almost certain to be influenced, even in many mild cases. Pulmonary valvulotomy has been established as a highly beneficial corrective procedure with a low operative mortality. Therefore the indications for operative inter-

vention in the optimum period of life may profitably be reconsidered. Further physiologic investigation, particularly studies of the circulatory dynamics, should be directed not only toward establishing a diagnosis but also toward clarifying operative indications at all ages, assessing more quantitatively the postoperative improvement and evaluating the risk and merit of alternative treatment programs.

SUMMARY AND CONCLUSIONS

Twenty-six cases of congenital pulmonic stenosis with intact ventricular septum are reported.

1. Symptoms were generally infrequent, inconspicuous and without relation to the magnitude of right ventricular hypertension.

2. The intensity of the systolic murmur was not grossly related to the severity of pulmonic stenosis. The valvular type was characteristically associated with a murmur in the second left interspace; murmurs heard best in other locations usually indicated involvement of the infundibulum of the right ventricle.

3. Exercise tolerance as reflected in the physical fitness index was unrelated to the severity of pulmonic stenosis.

4. Hyperventilation without dyspnea but with marked tachycardia during standard exercise suggested that breathing reserve is reduced but adequate for this stress and that cardiac output under stress is augmented by increasing heart rate with limited stroke volume. The infrequency of paradoxical responses suggests that pulmonary blood flow is increased during exercise, although in certain cases the increment may be limited by restriction of right ventricular outflow.

5. Pulmonic stenosis did not measurably interfere with cardiac output at rest.

6. In six cases cross-sectional area of flow of the pulmonic valve varied inversely with resistance which was reflected, in turn, by increased values for right ventricular work.

7. Right ventricular systolic hypertension and the gradient between right ventricular systolic and pulmonary artery systolic pressure were grossly related to the occurrence of right ventricular hypertrophy by electrocardiogram. However, the degree of right ventricular hypertension was not related to the volume of right to left shunt.

8. The mean pulmonary artery pressure is usually normal in resting patients.

9. The physiologic handicap and resulting reduction in cardiac reserve suggest the possible advantage of surgical correction, even of mild cases.

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Relationship of the Physiologic Third Heart Sound to the Jugular-venous Pulse*

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DURING a study of cardiovascular events in normal medical students the physiologic third heart sound was found to occur at the peak of the "V" wave in the jugular-venous pulse, rather than on the descending limb as was expected. The present communication presents these findings.

METHODS

Heart sounds, carotid pulses, jugular-venous pulses, electrocardiograms, as well as a careful history and physical examination, were obtained in sixty young adult medical students. No cardiac abnormality was noted in any of the subjects. A Cambridge 4-channel, direct writing recorder was principally used in the study. However, most of the subjects with the third heart sound were restudied at a later date, recording the heart sounds and jugular-venous pulses on a Sanborn twin-beam photographic oscillograph. Jugular pulses were obtained high in the neck and over the jugular bulb with the use of a glycerine capsule as well as with the suction-cup-type end piece. Care was used to obtain as "pure" a jugular pulse as possible. The importance of this will be presented subsequently. The time of the occurrence of the third heart sound, in relationship to the jugular-venous pulse, was identical with all types of recording technic used.

RESULTS

A third heart sound was recorded in eleven of sixty subjects. This was a very low-pitched sound following the second heart sound. It was best heard directly over the apex in the recumbent position. Figure 1 is a simultaneous record of phonocardiograms and jugular-venous pulses in three different individuals illustrating the time relationships of the third sound to the venous pulse. It can be noted that the onset of the third sound occurs with the peak of the "V" wave in the jugular pulse. However, since the sound had a

duration of approximately 0.04 seconds, the terminal portion of the vibration did occur on the early position of the descending limb of the

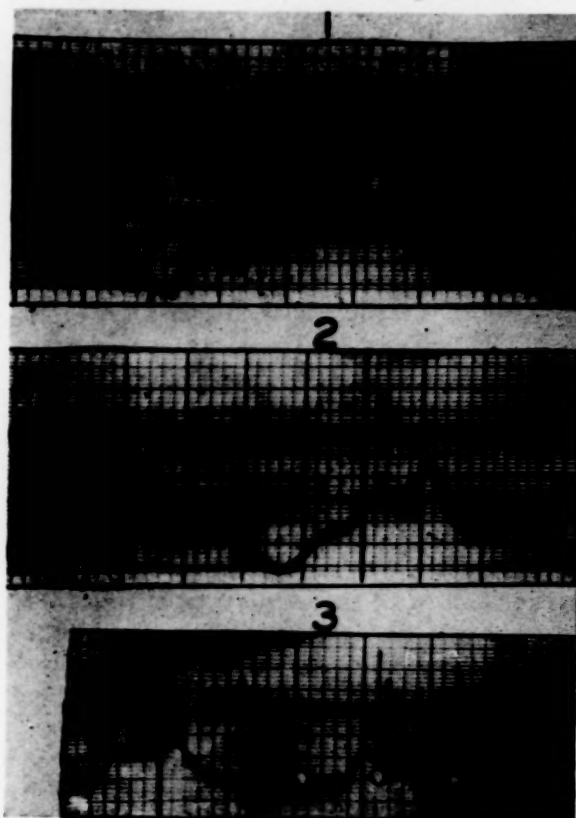


FIG. 1. Phonocardiograms from three normal subjects showing the time relationship of the physiologic third heart sound to the jugular-venous pulse. Note that the third heart sound occurs at the peak of the "V" wave, suggesting that it is produced at the time of the opening of the atrioventricular valves and is a "physiologic opening snap."

"V." The frequency of the sound was found to be approximately thirty vibrations per second, or just within the audible range.

COMMENTS

Since the work of Orias and Braun-Menendez,¹ and Osborn and Fath² the physiologic third

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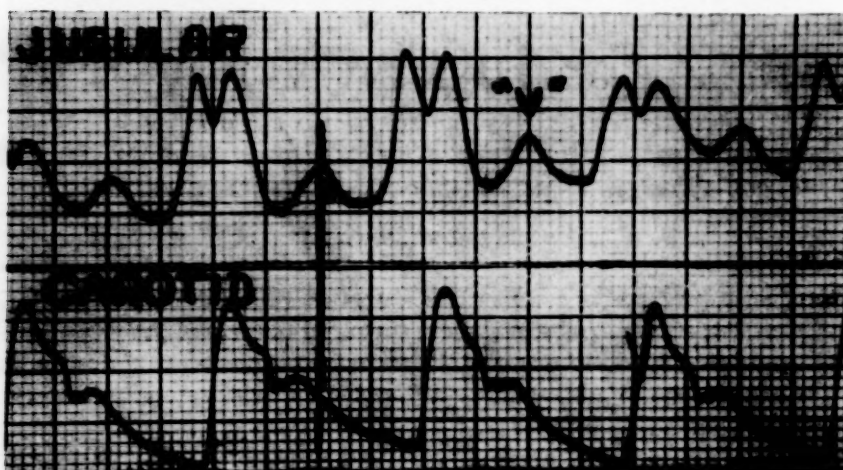


FIG. 2. A simultaneous record of the carotid pulse and jugular-venous pulse to illustrate the difference in time between the peaks of the dicrotic wave and the true "V" wave.

heart sound has been considered to occur during the period of maximal ventricular filling, which would correspond to the foot of the descending limb of the "V" wave of the jugular pulse. The present finding that the sound occurs at the peak of the "V" wave would suggest that it is produced by the opening of the atrioventricular valves; in other words, it is a "physiologic opening snap." This was postulated by Thayer many years ago as the mechanism for the physiologic third heart sound.^{3,4}

It is impossible to explain the apparent differences in timing of the occurrence of this sound, as reported in the literature, which contains few records of the third sound timed with jugular pulses. However, one suggestion may be offered. Technically, a "pure" jugular-venous pulse is difficult to obtain and most frequently elements of both carotid and venous pulses are registered. The outward movement following the carotid incisura or the aortic dicrotic wave may be confused with the jugular "V." If the peak of this wave is taken as the jugular "V" peak, the third sound will then fall on the descending limb and the period of isometric relaxation will have a duration of 0.06 to 0.08 seconds, or below the values generally accepted.⁵ Some tracings presented by Orias and Braun-Menendez had short periods for isometric relaxation.¹ Figure 2 is a simultaneous record obtained of a carotid and jugular pulse in one individual to show the difference in time of occurrence between the peak of the aortic dicrotic wave and the true peak of the "V" wave.

One criticism can be made of the present work,

to which we have no definite answer. We have been unable to determine the lag in time between the events taking place within the heart and those recorded in the jugular-venous pulse. In several subjects in whom auricular pressure curves were obtained during cardiac catheterization, no appreciable difference in time between the fall of the auricular pressure and the peak of the "V" wave was noted. It seems unlikely, however, that the time difference between the heart and the jugular events would be sufficient to place the third sound on the foot of the descending limb of the "V" wave, using the present recording technic.

CONCLUSION

The physiologic third heart sound was found in eleven of sixty young, normal subjects. The phonocardiographically recorded sound occurred at the peak of the "V" wave in the jugular-venous pulse, suggesting that the physiologic third heart sound is the result of the opening of the atrioventricular valves and is in reality a "physiologic opening snap."

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Clinical Studies with the Citrovorum Factor in Megaloblastic Anemia*

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IN 1948 a new substance¹ was discovered in liver extract and in yeast which was essential for the growth of *Leuconostoc citrovorum* 8081. The active principle was referred to as the citrovorum factor (CF). It was characterized as being distinct from vitamin B12 and pteroylglutamic acid (PGA) by its microbiologic and chemical properties.²⁻⁴ CF has the chemical structure of 5-formyl, 5,6,7,8-tetrahydropteroylglutamic acid. Its similarity to the structure of folic acid (PGA) immediately suggested a close metabolic relationship between these substances⁵ which has since been demonstrated.⁶ It was shown that the production of CF by liver slices of the rat was markedly increased in the presence of PGA or ascorbic acid and especially in the presence of both. The urinary excretion of CF was stated to be increased by the administration of PGA and to be further augmented by the simultaneous administration of ascorbic acid.⁷ It was shown that CF competitively reversed the lethal effects of aminopterin in mice when injected simultaneously with this folic acid antagonist.⁸ These and other experimental studies supported the concept that CF is a biologically active derivative of PGA and is, perhaps, the compound to which PGA must first be changed *in vivo* in order to exert its effect on metabolic processes.

It is chiefly in that group of diseases associated with a megaloblastic type of erythropoiesis that PGA and CF have demonstrated their clinical importance.⁹⁻¹⁴ Because both PGA and CF may induce hematologic remission in addisonian pernicious anemia, an anemia considered to be due to a deficiency of vitamin B12, one naturally seeks an understanding of the interrelationships between vitamin B12, PGA and CF.

This has not yet been clarified. It would appear however, that the vitamin B12 compounds (the cobalamins) and the "PGA-CF activity" substances (the pteroylglutamates) participate in nucleoprotein synthesis and are therefore critically concerned with metabolic processes which, if disturbed, can alter the integrity of all tissues of the body.

Clinical studies concerning the hemopoietic effects of these compounds have been retarded by the paucity of available patients with unaltered megaloblastic anemia. The recent reduction in the numbers of such patients seen in a general hospital can be attributed to the widespread use of orally effective hematinics which are readily available in multivitamin "shotgun" preparations. However, even sporadic case reports demonstrating the therapeutic characteristics of citrovorum factor under a variety of conditions can be useful and at times crucial in augmenting or confirming concepts derived from animal experimentation.

It is our purpose in this report to describe the effect of citrovorum factor administered to six patients ill with megaloblastic anemias of varied etiology.

METHODS AND RESULTS

Six patients ill with megaloblastic anemias on the wards of Kings County Hospital were the subjects of this study. Bone marrow examinations, gastric analyses for hydrochloric acid before and after stimulation with histamine, and complete blood studies were made in all patients. During the period of treatment daily reticulocyte counts and complete blood counts at least twice weekly were recorded. The reticulocytes were counted per 500 RBC, using the saline cresyl

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blue method. All red cell counts were made in duplicate, and the average count was recorded. Hematocrits were estimated using Wintrobe's technic. The hemoglobin was determined photocolorimetrically in alkaline solution, using a Coleman Jr. instrument. The CF* used in these studies contained 20 million units/ml., equivalent to 3 mg. of crystalline leucovorin/ml.

CASE REPORTS

A. Addisonian Pernicious Anemia (Vitamin B12 Deficiency)

CASE I. J. B., a sixty year old housewife, was admitted to Kings County Hospital for the first time on January 27, 1952, because of progressively increasing weakness, anorexia, pallor, dyspnea and weight loss of 16 to 20 pounds over a period of two months. The patient was known to have had hypertension for several years and was taking 0.1 mg. of digitoxin daily. There was no history of icterus, edema or of symptoms of combined system disease.

Physical examination: Temperature was 100.2°F.; pulse, 84; respirations, 28; blood pressure, 240/110. There was a definite icteric tinge to the face and sclerae. The liver and spleen were not palpable. Vibratory sense and position sense were intact. There was no peripheral edema.

Laboratory findings: On admission the hemoglobin was 4.2 gm. per cent; red blood cells 0.96 mil. per cu. mm.; hematocrit 14 per cent; MCV 145 cu. micra; MCH 43 gamma gamma; MCHC 30 per cent; reticulocytes 5.0 per cent; icterus index 12.5 units; white blood cells 4,250 per cu. mm. The stained smear showed moderate macrocytosis and moderate anisocytosis and poikilocytosis. Numerous hypersegmented neutrophils were seen. The bone marrow was megaloblastic. There was no free acid in the fasting gastric specimen or in the specimens obtained after histamine injection. The blood urea was 63 mg. per cent. The electrocardiogram suggested the presence of left ventricular hypertrophy.

Course: The patient was given no specific therapy until the initially elevated reticulocyte count had reached a normal level. One transfusion of 500 cc. of blood brought the red blood cell count to 1.17 mil. per cu. mm. The bone

marrow was still megaloblastic. On the tenth day the patient was given 3 mg. of vitamin B12 orally. The reticulocytes then reached a peak of 30.2 per cent five days later, and the red blood cells reached a level of 2.48 mil. per cu. mm. on the fourteenth day, at which time the patient was discharged to be followed in the clinic with maintenance therapy. However, she did not return for sixteen months. At that time her hemoglobin was 7.0 gm. per cent, and her red blood cell count was 1.89 mil. per cu. mm. A therapeutic regimen of 5 mg. of CF daily, orally, was started. In two months the hemoglobin rose to 13.5 gm. per cent and red blood cells to 4.05 mil. per cu. mm. Two months later, with no change in the hemoglobin or red blood cell count, severe tingling and paresthesias of both lower extremities developed, with diminished vibratory sense and position sense. One injection of 45 gamma vitamin B12 intramuscularly caused cessation of these symptoms and signs within a week. The patient has maintained a complete hematologic and neurologic remission while receiving 45 gamma B12 intramuscularly once monthly for five months.

Comment. When first seen this patient, who had addisonian pernicious anemia, had the expected maximal erythrocyte increase and reticulocyte response to the administration of vitamin B12. Several months later a partial relapse occurred because of failure of the patient to return for maintenance therapy. At this time 5 mg. of CF was given daily by mouth for four months. Despite return of the blood count to normal values signs and symptoms of fulminating combined system disease developed for the first time. Discontinuance of CF and initiation of parenteral vitamin B12 therapy resulted in disappearance of the neurologic symptoms within one week. It is interesting that this happens to be the only patient with addisonian pernicious anemia whom we have attempted to treat with a maintenance dosage of CF. The similarity of CF to PGA in the production of occasional deleterious effects on the central nervous system¹⁵ in pernicious anemia is worthy of note.

B. Nutritional CF Deficiency Superimposed on Addisonian Pernicious Anemia (B12 Deficiency)

CASE II. S. S., a seventy-three year old widow, was admitted to Kings County Hospital for the first time on May 22, 1950, because of anorexia, progressively increasing exertional dyspnea and ankle edema, intermittent bouts of

* The CF (leucovorin®) was generously supplied to us by Dr. J. Reugsegger of the Lederle Laboratories Division of the American Cyanamid Corporation, Pearl River, N. Y.

vomiting and diarrhea, and pallor and coldness of the extremities, all of which started about five months prior to hospitalization. The patient had lost about 25 pounds during this period. There was no history of blood loss or of neurologic aberrations.

Physical examination: Temperature was 100.2°F.; pulse, 80; respirations, 20; blood pressure, 130/50. The patient was very thin. She appeared chronically ill but was alert. The skin had a lemon yellow tinge and the sclerae were icteric. There were fine crepitant rales at the bases of both lungs, more prominent on the right side. The heart was enlarged and auricular fibrillation at a slow rate was evident. There was a soft systolic murmur at the pulmonic area. There was 2+ pitting edema of the lower extremities.

Laboratory findings: Four days after admission the hemoglobin was 3.7 gm. per cent; red blood cells 0.93 mil. per cu. mm.; hematocrit 11.5 per cent; MCV 123.5 cu. micra; MCH 39 gamma gamma; MCHC 32 per cent; reticulocytes 1.9 per cent; icterus index 7 units; white blood cells 3,600 per cu. mm. The stained smear showed macrocytosis, poikilocytosis, anisocytosis and polychromatophilia. Numerous macropolocytes and eleven megaloblasts per one hundred leukocytes were seen in the smear of peripheral blood. The gastric analysis revealed no hydrochloric acid after an injection of histamine.

Course: The patient received 500 cc. of packed red blood cells intravenously on May 25th and 26th. On May 29th the red blood count was 1.81 mil. per cu. mm.; hemoglobin 5.9 gm. per cent; hematocrit 18 per cent. The patient was given 0.5 mg. of PGA by mouth on May 27th and daily thereafter for ten days. There was no reticulocyte response to this therapy, nor did the red cell count rise. On June 6th a blood transfusion of 250 cc. packed red cells was given, PGA was stopped and 10 gamma of vitamin B12 by mouth was given daily for a second ten-day period, again without response. On June 16th combined oral therapy of 0.5 mg. PGA and 10 gamma of vitamin B12 was started and continued for another ten days, again without response. On June 26th the patient received 60 gamma of vitamin B12 intramuscularly. Reticulocytosis started on the fourth day and reached a peak of 14 per cent on the sixth day. Blood values rapidly approached normal levels and the patient was discharged to a nursing home on July

12, 1950, with instructions that she be given 60 gamma of vitamin B12 by injection at least once a month.

Second admission: The patient was admitted for the second time eighteen months later, on December 4, 1952, in a semi-comatose state, with the history that she had been receiving liver in capsule form only. In addition she had eaten almost no solid food during the three months prior to her admission. The patient was having frequent bulky loose stools.

Physical examination: The patient was semi-comatose and cachectic. The skin and sclerae were pale and icteric. Temperature was 100°F.; pulse, 120, irregular; respirations, 28; blood pressure, 110/70. There were coarse rales at both lung bases. Auricular fibrillation was present with a pulse deficit of 18.

Laboratory examination: On admission the hemoglobin was 2.5 gm. per cent; red blood cells 0.58 mil. per cu. mm.; hematocrit 7 per cent; MCV 120 cu. micra; MCH 43 gamma gamma; MCHC 35.7 per cent; reticulocytes 0.3 per cent; icteric index 40 units; white blood cells 4,250 per cm. The sternal marrow was megaloblastic. Her gastric juice contained no free HCl after histamine stimulation. Pepsin was also absent.

Course: A transfusion of 500 cc. of packed red cells was given on December 4, 1952. Vitamin B12, 60 gamma intramuscularly, was given initially on the same day and 30 gamma daily thereafter for seven days. On December 8th the red count was 1.62 mil. per cu. mm.; hemoglobin 4.3 gm. per cent; hematocrit 11 per cent. The patient received a transfusion of 250 cc. of packed red cells. On the eighth day a reticulocytosis had not yet occurred. Vitamin B12 was discontinued, another 250 cc. transfusion of packed red cells was administered and CF, 6 mg./day intramuscularly, was started. Following the last transfusion the red count was 2.26 mil. per cu. mm. On December 15th, the fifth day of CF treatment, a reticulocyte peak of 8.7 per cent was reached. On the nineteenth day the red blood cell count had risen to 3.64 mil. per cu. mm. (Fig. 1.) The patient was then transferred to another hospital for custodial care.

Comment. This patient with Addisonian pernicious anemia, first studied in 1950, failed to respond to a ten-day treatment period of 0.5 mg. PGA and 10 gamma of vitamin B12 by mouth daily. However, subsequent administration of 60 gamma vitamin B12 intramuscularly daily

resulted in an excellent hematologic remission. Because of a senile psychosis she was taken to an old ladies' nursing home where, unfortunately, no further vitamin B12 therapy was given during the next two years. The patient ate very little food of any sort. On December 4, 1952, (Fig. 1)

this patient had a nutritional vitamin B12 deficiency originally, and that later a nutritional CF deficiency was added. The achylorhydria would then be a non-related incidental finding and the absence of pepsin in the gastric juice would be unexplained.

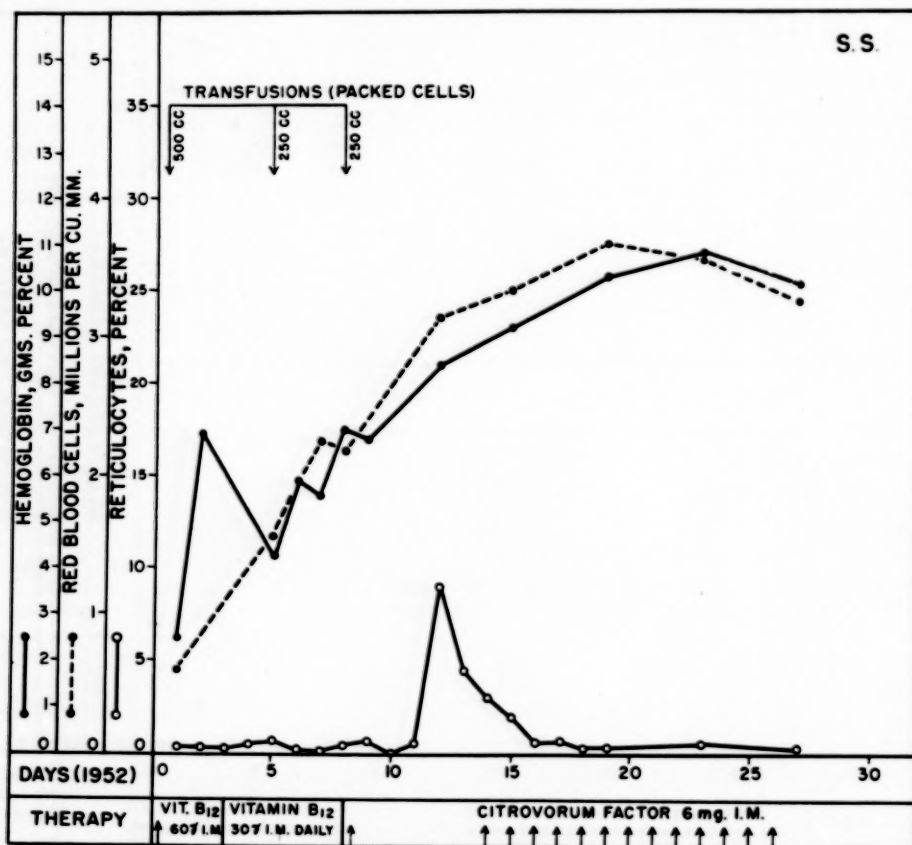


FIG. 1. Case II.

she was brought back to the hospital in a moribund state, with a red blood cell count of only 0.58 mil./cu. mm. This time parenteral administration of vitamin B12 produced no improvement whatsoever. Subsequent parenteral therapy with CF produced a definite, though suboptimal, hematologic response. It was thought that failure to respond to vitamin B12 treatment in the preceding eight-day period may have been due to the fact that an additional complete nutritional deficiency of CF had inhibited the expected response. The excellent response to B12 two years previously was typical of that seen in Addisonian pernicious anemia. Furthermore, the absence of pepsin in the gastric juice, in addition to the absence of HCl, suggested true achylia gastrica. Otherwise, an alternative explanation (which seems less likely to us) is that

C. Nutritional Megaloblastic Anemia Due to CF Deficiency

CASE III. B. C., a forty-two year old white housewife, was admitted to Kings County Hospital for the first time on March 29, 1952, because of weakness and malaise during the four months prior to admission. On admission the patient was confused. The history subsequently obtained from the family indicated that the patient consumed large quantities of alcohol and ingested very little solid food. There was no history of blood loss or icterus. Paresthesias of the hands and feet had been noted during the month prior to hospitalization.

Physical examination: Temperature was 99°F.; pulse, 90; respirations, 20; blood pressure, 122/66. The patient appeared extremely pale

and both acutely and chronically ill. The tongue was smooth and shiny. The liver edge was felt 2 cm. below the right costal margin and was firm and non-tender. The spleen was not palpated. Neurologic examination was negative.

Laboratory findings: On admission the patient

ally approached normal levels and on the day of discharge, the thirtieth day of treatment, the hemoglobin was 10.9 gm. per cent; red blood cells 3.69 mil. per cu. mm.; hematocrit 36 per cent. The patient's clinical improvement was slow and on two occasions temperature up to

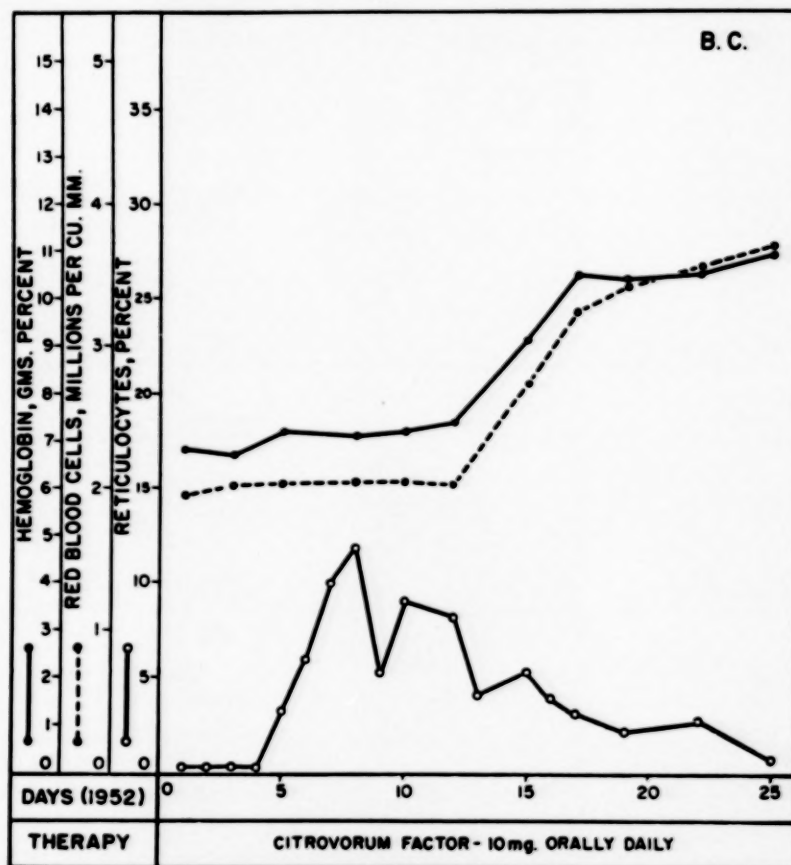


FIG. 2. Case III.

received 1,500 cc. of whole blood after which, on March 29th, the hemoglobin was 6.8 gm. per cent; red blood cells 1.96 mil. per cu. mm.; hematocrit 20 per cent; MCV 102 cu. micra; MCH 34 gamma gamma; MCHC 34 per cent; reticulocytes 0.6 per cent; icterus index 20 units; white blood cells 2,400 per cu. mm. The stained smear of the peripheral blood showed macrocytosis, anisocytosis and poikilocytosis of the red cells. There were numerous macropolycytes. The sternal marrow was megaloblastic. There was free acid in a specimen of gastric contents after histamine. The urine was normal.

Course: On March 31st the patient was started on a regimen of 10 mg. CF orally per day. On the fifth day of therapy reticulocytosis was noted and reached a maximal peak of 12 per cent on the eighth day of treatment. Blood values gradu-

ally approached normal levels and on the day of discharge, the thirtieth day of treatment, the hemoglobin was 10.9 gm. per cent; red blood cells 3.69 mil. per cu. mm.; hematocrit 36 per cent. The patient's clinical improvement was slow and on two occasions temperature up to

104.8°F. was noted, the cause of which could not be determined. (Fig. 2.)

Comment. This patient had a very poor dietary intake associated with a high alcoholic intake. Free HCl was present in her gastric secretion. Her megaloblastic anemia, which was presumably due to a nutritional deficiency, responded excellently to CF.

CASE IV. J. T., a sixty-two year old unemployed man, was admitted to the hospital for the first time on June 28, 1951. He was known to have had hypertension for many years, and in the month prior to admission progressively increasing dyspnea, orthopnea and weakness developed. His dietary intake had been inadequate for many months.

Physical examination: Temperature was 101.2°F.; pulse, 100; respirations, 30; blood

pressure, 140/70. The patient was poorly nourished and very pale. He was moderately dyspneic at rest. The heart was slightly enlarged to the left and a soft systolic murmur was heard at the apex. Bilateral basal rales were heard on auscultation of the chest. There was no hepato-

changed. The patient was then given a single injection of 90 gamma vitamin B12 intramuscularly and one blood transfusion. Again there was no reticulocyte rise in the next ten days. The patient was then given 1.5 mg. CF by intramuscular injection daily. On the seventh

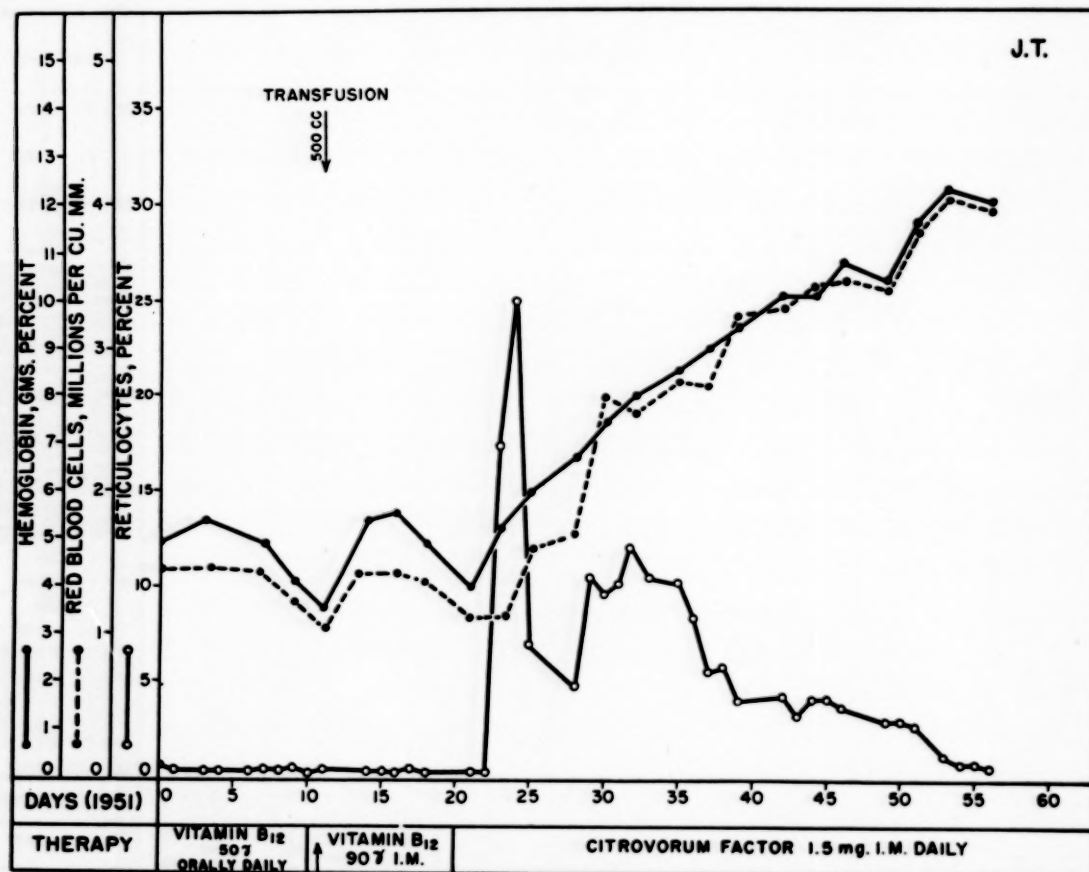


FIG. 3. Case IV.

megaly or splenomegaly. No icterus or edema was present. Vibratory sense and position sense were intact. The deep reflexes were active.

Laboratory findings: On admission the hemoglobin was 4.9 gm. per cent; red blood cells 1.42 mil. per cu. mm.; hematocrit 13 per cent; MCV 91.5 cu. micra; MCHC 37.6 per cent; MCH 34.5 gamma gamma; reticulocytes 0.8 per cent; icterus index 7.5 units; white blood cells 2,400 per cu. mm. with a normal differential count. The bone marrow was megaloblastic. Gastric analysis showed the presence of free acid in the gastric secretions thirty minutes after an injection of histamine was given.

Course: The patient was given 50 gamma of vitamin B12 orally, daily for ten days, but no reticulocyte response was observed. The hemoglobin and red blood cell values remained un-

changed. The patient was then given a single injection of 90 gamma vitamin B12 intramuscularly and one blood transfusion. Again there was no reticulocyte rise in the next ten days. The patient was then given 1.5 mg. CF by intramuscular injection daily. On the seventh

day a reticulocyte peak of 25.0 per cent was reached and the red blood cells began to rise. On discharge, thirty-seven days after the first injection of CF, the hemoglobin was 12.0 gm. per cent; red blood cells 3.83 mil. per cu. mm.; hematocrit 37 per cent; MCV 95 cu. micra; MCHC 32 per cent; MCH 30 gamma gamma; reticulocytes 1.0 per cent; icterus index 5 units; white blood cells 4,100 per cu. mm. (Fig. 3.)

Comment. The initial failure of the patient to respond to B12, and the subsequent response to CF, indicated a nutritional deficiency of CF rather than of vitamin B12.

CASE V. L. E., a fifty year old white waiter, was admitted to Kings County Hospital for the first time on February 27, 1952, because of progressively increasing malaise, weakness and loss of appetite for eight months prior to hospital-

ization, and diarrhea intermittently for six weeks before admission. During the previous four years the patient had consumed 11 to 12 ounces of whiskey a day. In June 1951, he had been hospitalized elsewhere and transfused with 8 pints of blood. There was no history of blood loss, jaundice or nervous system disorder.

sisted even after histamine stimulation. The blood urea was 50 mg. per cent; cholesterol 130 mg. per cent; plasma protein 7.6 gm. per cent; albumin 5.2 gm. per cent; globulin 2.4 gm. per cent; alkaline phosphatase 1.7 Bodansky units. There was 30 per cent retention of BSP dye at forty-five minutes. The prothrombin time was

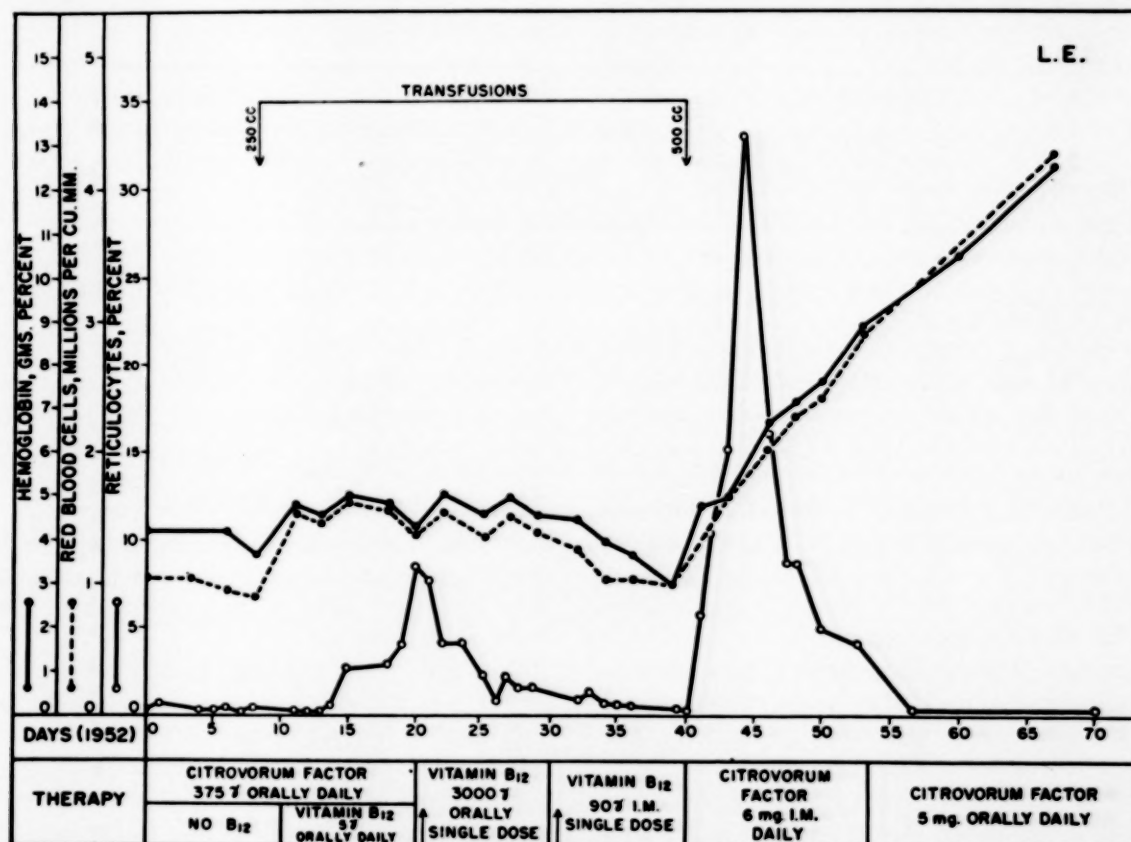


FIG. 4. Case v.

Physical examination: Temperature was 100°F.; pulse, 120; respirations, 20; blood pressure, 122/40. The skin and mucous membranes were pale. The tongue margins were atrophic. The liver edge extended 3 cm. below the right costal margin and the spleen tip was palpated 1 cm. below the left costal margin.

Laboratory findings: On admission the hemoglobin was 4.2 gm. per cent; red blood cells 1.04 mil. per cu. mm.; hematocrit 12 per cent; MCV 151 cu. micra; MCH 40 gamma gamma; MCHC 35 per cent; reticulocytes 0.8 per cent; icterus index 10 units; white blood cells 3,500 per cu. mm. The stained smear of the peripheral blood showed macrocytosis, anisocytosis and poikilocytosis of red cells. There were occasional macropolycytes. The bone marrow from the sternum was megaloblastic. Achlorhydria per-

17.5 seconds, with the control 14.0 seconds. The Mazzini test was negative. Biopsy of the liver showed periportal fibrosis with hemosiderin deposition in the sinusoids and Kupffer cells.

Course: The patient was placed on a diet free of meat, eggs, fish and cheese. On February 29th he was started on a ten-day course of oral CF, 375 gamma per day. There was no reticulocyte response. After transfusion of 250 cc. packed red cells on March 7, 1952, the red count was 1.5 mil. per cu. mm.; hemoglobin 5.0 gm. per cent; hematocrit 15 per cent. On March 10th therapy was altered to include 375 gamma of CF and 5 gamma of vitamin B₁₂ daily by mouth. This was given for ten days. On the fifth day the reticulocytes rose to 2.6 per cent, reaching a peak of 8.4 per cent on the tenth day. At this point therapy was discontinued and 3,000

gamma (3 mg.) of vitamin B12 in the form of a single oral dose was given. No further reticulocyte response occurred in the next ten days. On March 28th 90 gamma of vitamin B12 was administered intramuscularly. No reticulocyte response took place during the next ten-day period. Furthermore, no rise of red cells had occurred at any time. On April 7th, following these tests and forty days after hospitalization, the sternal marrow obtained by aspiration was still megaloblastic. A transfusion of 500 cc. whole blood given on April 7th raised the red count from 1.0 to 1.6 mil. per cu. mm. On that same day, therapy with 6 mg. of CF by daily intramuscular injection was initiated. On the third day of CF treatment a reticulocytosis of 6.2 per cent occurred, and reached a peak of 32.8 per cent on the fifth day of therapy. Throughout the entire period of hospitalization the patient was afebrile. He was drowsy and weak until March 15th when he began to improve slowly. He became ambulatory on April 12th. He was discharged on April 21, 1952, with instructions to take 5 mg. of CF by mouth every day. The red blood cell count was 4.98 mil. per cu. mm. on the twenty-eighth day of therapy. (Fig. 4.) When the patient was last seen in the clinic nine months later, his blood counts were normal.

Comment. This patient, who was a chronic alcoholic, had been eating very little food for eight months prior to admission. He had no neurologic disorder. Liver function tests were abnormal and portal cirrhosis of the liver was diagnosed by biopsy. It was decided to treat his megaloblastic anemia with very small doses of CF in order to establish a minimally effective therapeutic dose. He was given 375 gamma of CF daily by mouth for ten days without any reticulocyte response. The addition of 5 gamma of vitamin B12 daily by mouth for another ten days resulted in no significant hematologic clinical response.

His subsequent failure to respond to 3 mg. of vitamin B12 by mouth and then to 90 gamma of vitamin B12 by injection demonstrated that he had no deficiency of vitamin B12 and therefore could not have had addisonian pernicious anemia. The achlorhydria was then interpreted as not indicative of achylia gastrica and not pathogenetically related to the megaloblastic anemia. The final excellent results obtained by daily parenteral injections of CF clearly establish the presence of a nutritional CF deficiency in this patient. The initial failure to respond to

375 gamma of CF by mouth can then be interpreted as due to the very small amounts used.

D. Nutritional Megaloblastic Anemia Due to Deficiency of CF and Vitamin B12

CASE VI. P. C., a fifty-five year old Italian man, was admitted to Kings County Hospital for the first time on May 24, 1950, because of progressively increasing dyspnea, ankle edema, anorexia and abdominal pain in the right upper quadrant of four months' duration.

For many years the patient drank unusually large amounts of wine daily and his dietary intake had been relatively inadequate. There was no history of jaundice or change in color of his urine.

Physical examination: Temperature was 100.4°F.; pulse, 110; respirations, 30; blood pressure, 136/70. The patient was fairly well nourished but was very pale. Moderate dyspnea was present at rest. Rales were heard anteriorly and posteriorly over the bases of both lung fields. The liver was palpated 8 cm. below the costal margin and was tender. The spleen was not palpable. There was 4+ pitting edema of both lower extremities. The vibratory sense and position sense were intact. The deep reflexes were normal.

Laboratory findings: On admission the hemoglobin was 5.8 gm. per cent; red blood cells 2.0 mil. per cu. mm.; hematocrit 20.5 per cent; MCV 1025 cu. micra; MCH 29.2 gamma gamma; MCHC 28.2 per cent; reticulocytes 0.4 per cent; icterus index 7 units; white blood cells 7,250 per cu. mm. with a normal differential count. The stained smear showed moderate macrocytosis, anisocytosis and poikilocytosis. The marrow was megaloblastic. The urine was normal except for Ehrlich's aldehyde reaction for urobilinogen which was positive to a dilution of 1:60. The gastric contents contained no free acid either in the fasting specimen or in the specimens up to two hours after a histamine injection was given. The cephalin flocculation test was 2+. The Mazzini test was negative.

Course: The patient was thought to have addisonian pernicious anemia and was given a single dose of 60 gamma vitamin B12 intramuscularly. On the third day after this injection the reticulocytes began to rise and reached a peak of 11 per cent on the sixth day. The hemoglobin rose to 7.5 gm. per cent and the red blood cells to 3.2 mil. per cu. mm. on the tenth day. The patient was discharged to the Hematology

Clinic where he received 45 gamma of B12 intramuscularly once a month for the next two years.

Six months after he was discharged the hemoglobin was 13.1 gm. per cent and the red blood cells were 6.09 mil. per cu. mm. For the following seventeen months the hemoglobin remained

not palpable. There was 4+ pitting edema of both lower extremities.

Laboratory findings: The blood examination on admission showed: hemoglobin 6.0 gm. per cent; red blood cells 1.94 mil. per cu. mm.; hematocrit 18 per cent; MCV 92 cu. micra;

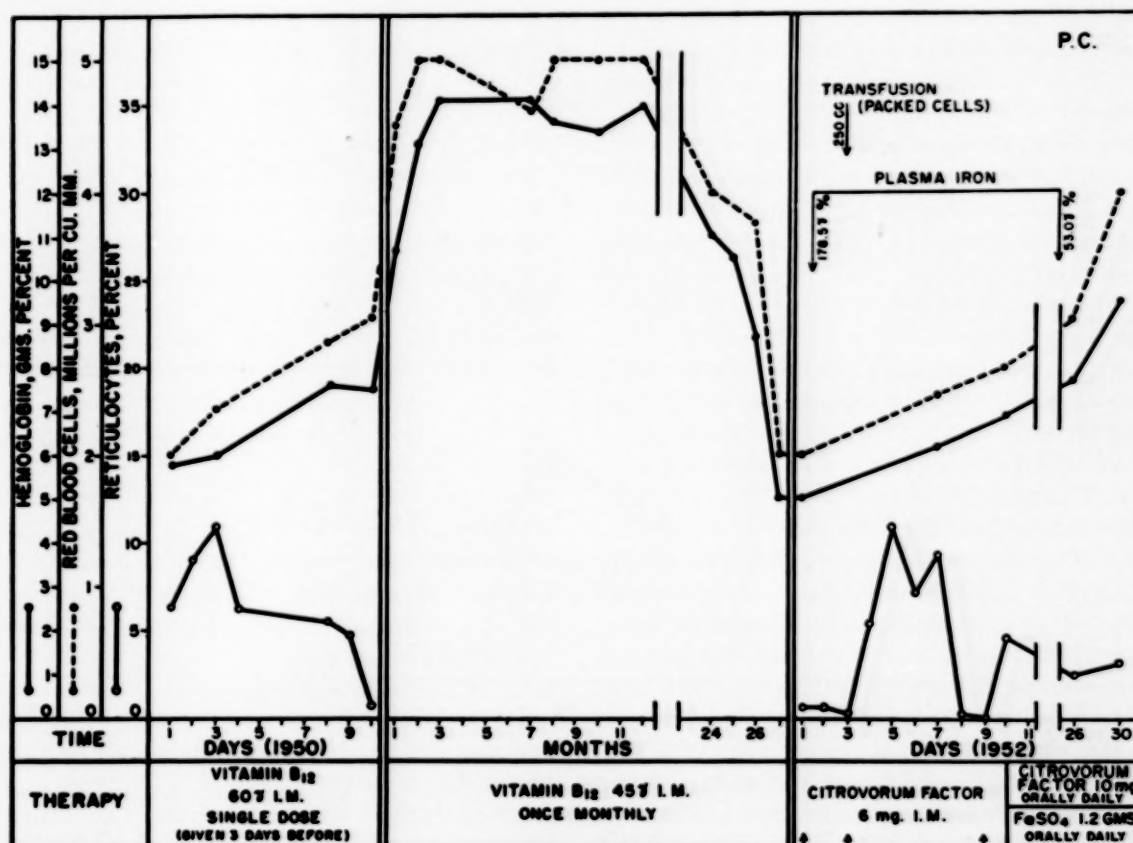


FIG. 5. Case VI.

between 13 and 14 gm. per cent and the red blood count between 4 and 6 mil. per cu. mm. On the twenty-fourth month after the first admission the patient began to feel weak and it was found that the hemoglobin had dropped to 11.0 gm. per cent despite continuation of the monthly injections of B12. For the next three months the hemoglobin gradually dropped to 5.0 gm. per cent and the red blood cells to 2.0 mil. per cu. mm. (Fig. 5.)

Second admission: The patient became weaker and had progressively increasing dyspnea and peripheral edema. He became icteric and was readmitted to the hospital on October 22, 1952.

Physical examination: Bilateral basal rales were heard on auscultation of the chest. Ascites was present. The liver was palpated 10 cm. below the right costal margin. The spleen was

MCHC 33 per cent; MCH 30.9 gamma gamma; reticulocytes 0.6 per cent; icterus index 20 units; white blood cells 9,800 per cu. mm. The marrow was megaloblastic. The urine was negative except for Ehrlich's aldehyde reaction for urobilinogen which was positive to a dilution of 1:100. Gastric analysis showed no free acid in the fasting specimen but did show free acid fifteen minutes after a histamine injection was given. The Coombs test was negative. The BSP test showed 30 per cent retention at fifteen minutes and 21 per cent retention at thirty minutes. The plasma iron was 178.5 gamma per cent. The alkaline phosphatase was 4.7 Bodansky units.

Course: The patient was given 6 mg. of CF intramuscularly, followed two days later by a transfusion of 250 cc. of packed red cells and a

second injection of 6 mg. of CF. On the third day the reticulocytes began to rise, reaching a peak of 11 per cent on the fifth day. On the tenth day after therapy the hemoglobin was 7.0 gm. per cent and the red blood cells 2.68 mil. per cu. mm. The patient then refused further hospitalization and signed his release. On leaving the hospital he was instructed to take 10 mg. CF daily by mouth. Because of a drop in plasma iron to 53 gamma per cent he was also started on 1 gm. of ferrous sulfate daily. When seen in the clinic two months after his second admission, he felt markedly improved. His hemoglobin was 12.0 gm. per cent and his red blood cells were 4.40 mil. per cu. mm. (Fig. 5.) When he was seen six months later (on June 10, 1953), he had considerable ascites but felt well. The blood values remained unchanged.

Comment. In 1950 this fifty-five year old man was found to have a megaloblastic anemia associated with histamine-fast achlorhydria. There was no evidence of combined system disease. The patient was a heavy wine drinker who ate relatively little food. His liver was enlarged to 8 cm. below the costal margin. A single intramuscular injection of 60 gamma of vitamin B12 resulted in complete hematologic and clinical remission which can be interpreted only as evidence of vitamin B12 deficiency. Two years later, in 1952, the patient had a relapse while receiving adequate amounts of vitamin B12 as maintenance therapy but while on a grossly inadequate dietary intake. This time free HCl was shown to be present in the gastric juice. The cirrhosis of the liver had progressed and ascites had developed in the interim. The megaloblastic anemia responded well to CF therapy, indicating the presence of CF deficiency. The original vitamin B12 deficiency can be explained either (1) as a result of poor absorption of B12 because of an atrophic gastric mucosa due to addisonian pernicious anemia, or (2) as a result of a poor dietary intake of vitamin B12. Addisonian pernicious anemia seems unlikely, since the second gastric analysis showed the presence of free HCl and because of the absence of combined system disease. Furthermore, cirrhosis of the liver is rarely associated with addisonian pernicious anemia, whereas it is commonly associated with a nutritional megaloblastic anemia because of the frequency of poor nutrition. The continuance of vitamin B12 maintenance therapy for many months, during which time the dietary intake was very poor, may have hastened the

development of the CF deficiency. When the CF deficiency was complete, the megaloblastic anemia relapsed in spite of B12 therapy, and then responded only to the administration of CF.

DISCUSSION

It is well known¹⁶⁻¹⁸ that most patients who have addisonian pernicious anemia will show an adequate hematologic response to the administration of citrovorum factor, and six such cases have been previously reported by us.⁹ These reports were concerned with immediate results within the first few weeks of therapy and did not include studies over a long period of time. However, Meyer and Diefenbach¹⁹ cited a patient in whom combined system disease developed after three months of treatment with CF given orally, despite maintenance of a normal blood picture. In our patient (Case 1), who is similar, a neurologic relapse developed after four months of therapy with CF given orally, also at a time when the red blood cell count was normal. A quantitative comparison of the frequency of the neurologic complications occurring while using CF will probably not be forthcoming, since the use of CF as maintenance therapy for patients who have addisonian pernicious anemia would seem definitely contraindicated.

Pteroylglutamic acid has been shown to have a harmful effect on the nervous system^{15,20} under such circumstances and it is not surprising that CF behaves in a similar manner. This is in contrast to the beneficial effect of vitamin B12 on combined system disease. It is possible that the hematologic response to CF or PGA may further deplete the already sparse body stores of vitamin B12 to a critically low level, at which time the severe deficiency of B12 results in accelerated development of combined system disease. The time required for this depletion may be quite variable, since some patients have not had a neurologic relapse until as long as three years after treatment with PGA. Little is known about the time interval in the case of treatment with CF. Moore et al.²¹ reported a patient whose neurologic as well as hematologic abnormalities were controlled by therapy with CF for five months. A longer period of observation will be necessary for complete evaluation of this patient.

Five of the patients reported responded to treatment with citrovorum factor in a manner suggesting that a nutritional deficiency for this substance was present. Presumably in every

instance in which citrovorum factor was effective there would have been an equally good response had a comparable amount of pteroylglutamic acid been administered instead. But, had PGA been given instead of CF the presence of a maximal response to treatment with PGA would have made subsequent administration of CF impossible to evaluate. The double reticulocyte response is useful only when one substance is much more hematologically effective than another. One means of comparing PGA with CF is to compare, weight for weight, their minimally effective therapeutic doses. However, since individual patients vary so much in their responses to the same drug a large number of cases would be necessary for statistical comparison and it is virtually impossible for a single investigator to accumulate a large enough series of case records of nutritional megaloblastic anemia to be of statistical significance.

Jarrold *et al.*¹⁸ concluded that CF was no more effective than PGA in pernicious anemia in relapse (three cases). Woodruff, Peterson and Darby¹¹ could not come to a definite conclusion as to whether CF or PGA was more active in the treatment of non-scorbutic megaloblastic anemias of infancy (four cases). Romero *et al.*¹⁰ thought that, weight for weight, CF was ten to fourteen times as active as PGA in nine cases of megaloblastic anemia due to sprue. They obtained good results in five of six cases with as little as 1 mg. of CF in a daily intramuscular dose. However, it might be said parenthetically that the minimally effective dose of PGA in sprue has not been definitely established. The smallest intramuscular dose of CF which we used was 1.5 mg. daily, in Case iv, and that produced a maximal hematologic response. In Case v, 375 gamma of CF orally daily was essentially ineffective. Further investigation of nutritional megaloblastic anemia using small amounts of CF could yield valuable information concerning its relative effectiveness compared with PGA.

To date, no case of megaloblastic anemia has been reported with initial failure to respond to CF, followed by response to PGA, or vice versa. In other words no specific CF deficiency different from PGA deficiency has been found. One possible exception may be the megaloblastic anemia of scurvy. Since ascorbic acid is important in effecting the reduction of PGA to CF,⁶ in the absence of ascorbic acid, CF would be expected to be the more effective therapeutic agent in the treatment of the megaloblastic anemia of scurvy.

Indeed, that may be the one example of an isolated CF deficiency. This possibility awaits clinical demonstration. In the other types of megaloblastic anemia occurring in man CF has not been found to be either less or more effective than PGA in treatment.

Theoretically, dual deficiencies of CF and vitamin B12 in the same patient would be possible, although this has not been reported. It is therefore of some interest that two of our patients apparently illustrate this point. One patient (Case ii) has addisonian pernicious anemia (vitamin B12 deficiency) and originally was improved by therapy with vitamin B12. Later a superimposed nutritional deficiency developed with a megaloblastic relapse. This time a hematologic remission could not be obtained until CF was given.

The other patient (Case vi) had a nutritional megaloblastic anemia associated with Laennec's cirrhosis of the liver. The administration of vitamin B12 resulted in complete hematologic remission originally, but later, as the diet became more inadequate, relapse occurred despite continued injections of vitamin B12. Treatment with CF resulted in another remission. This patient, then, first had a dietary deficiency of vitamin B12 and a deficiency of CF later developed.

The diagnosis of addisonian pernicious anemia depends on the finding of a macrocytic anemia, megaloblastic erythroid precursors in the bone marrow and achylia gastrica. The development of this disease may be considered to be due to a deficiency of absorbed vitamin B12 secondary to the absence of "intrinsic factor" in the gastric secretions. Parenteral administration of vitamin B12 or oral treatment with vitamin B12 plus "intrinsic factor" affords complete replacement therapy. The test for the presence of "intrinsic factor" in gastric secretions is technically too inconvenient to be of value from a clinical point of view. The finding of the presence of free hydrochloric acid in a specimen of gastric juice obtained fifteen to forty-five minutes after injection of histamine is reasonably good evidence for eliminating the diagnosis of addisonian pernicious anemia. When the gastric analysis fails to reveal the presence of free hydrochloric acid, one can only conclude that addisonian pernicious anemia is a possible diagnosis since achlorhydria without true achylia gastrica is not uncommon in the older age groups. In such patients the finding of evidence of posterolateral sclerosis confirms the diagnosis because of the rarity of

such spinal cord changes in other types of megaloblastic anemia.

In megaloblastic anemias with associated gastric achlorhydria vitamin B12 is the drug of choice. When hydrochloric acid is found in the gastric juice, treatment with citrovorum factor or pteroylglutamic acid is indicated. This was demonstrated in three of our patients (Cases III, IV and V). In rare instances dual deficiencies may co-exist (Cases II and VI).

SUMMARY AND CONCLUSIONS

1. Therapy with CF for four months given to a patient with addisonian pernicious anemia resulted in acute combined system disease which cleared up promptly upon changing the treatment to the parenteral administration of vitamin B12. The use of CF (like PGA) is undoubtedly contraindicated in addisonian pernicious anemia.

2. Five patients with nutritional megaloblastic anemia had hematologic remissions after therapy with CF. Four of them had previously failed to improve when given vitamin B12.

3. Two patients apparently had dual deficiencies of both vitamin B12 and CF: (a) In one patient (Case II) with addisonian pernicious anemia (vitamin B12 deficiency) a superimposed deficiency of CF developed; (b) one patient (Case VI), who had cirrhosis of the liver and a nutritional megaloblastic anemia, had a good hematologic remission initially when given vitamin B12 but subsequently relapsed and responded only to the administration of CF.

4. CF is comparable to PGA in its clinical usefulness and can be expected to be efficacious in the treatment of nutritional megaloblastic anemia.

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Hematologic Studies on Patients with Sickle Cell Anemia Following Multiple Transfusions*

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THE remarkable increase in our knowledge of the pathologic physiology of sickle cell anemia in recent years has suggested that multiple blood transfusions might act as exchange transfusions in the treatment of this disease. For this reason it was decided to study the hematologic effects of multiple transfusions in a group of patients with sickle cell anemia. The results of this study are the subject of this report. We have found in the literature only two case reports^{1,2} that have been concerned with this problem.

MATERIAL AND METHODS

The patients with sickle cell anemia were hospitalized for study beginning at least four days prior to transfusion to obtain baseline values. Transfusions of bank blood preserved with acid-citrate-dextrose mixture then were given at intervals of one or two days until the erythrocyte count reached normal. While the patients were hospitalized, determinations of the erythrocytes, reticulocytes, sickled cells and plasma bilirubin were made three times a week and, as far as possible, all stools were collected for determinations of urobilinogen. After discharge from the hospital the patients were followed at weekly intervals for varying periods.

Erythrocyte counts were made in the usual manner with counting chambers and pipettes certified by the U. S. Bureau of Standards. Reticulocytes were stained with aqueous brilliant cresyl blue and the percentage was determined after a count of 1,000 erythrocytes. Absolute numbers were calculated from erythrocyte counts made at the same time. The number of sickled erythrocytes was estimated by means of the bisulfite method of Daland and

Castle.³ A drop of blood was mixed with a large drop of bisulfite solution on a slide and the mixture was covered with a number zero cover glass. After the preparation had stood for fifteen minutes, 1,000 erythrocytes were examined in various fields and the percentage of sickled cells, both crescentic and "holly wreath" forms, was determined. By means of this percentage figure the total number of sickled erythrocytes was calculated from the erythrocyte count made at the same time. In one patient the number of sickled cells was not estimated in this manner. In this first patient studied the number of sickled cells recorded was the number counted directly in the chamber when the erythrocyte determination was made. For this reason the initial sickle cell count was lower than that obtained in the other patients by the Daland and Castle method. Plasma bilirubin was measured by the Malloy and Evelyn⁴ modification of the method of Ducci and Watson.⁵ Fecal urobilinogen was determined by the method of Schwartz, Sborov and Watson.⁶ All stools were collected and the determinations were expressed as daily averages in each four-day period. Blood volumes were determined by the Evans blue dye method of Nitsche and Cohen.⁷

Satisfactory stool collections were not obtained from two of the subjects. Multiple transfusions were given to two patients on two occasions and the effects on the erythrocyte count on both occasions are shown in the figures. The number of sickle cells was not determined at the time of the first series of transfusions.

RESULTS

Seven transfusion studies were made in five patients with sickle cell anemia. The base

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line data for these subjects are shown in Table I.

The initial erythrocyte counts varied from 1.4 million per cu. mm. to 2.7 million per cu. mm. The changes that followed transfusions are shown in Figure 1. The normal range of 4.5 to

an eighteen months old child to 2,500 cc. given to a nineteen year old male who weighed 70 pounds. No transfusions were given after the blood count had been brought to normal. The erythrocyte count began to fall soon after the normal range was reached. The counts declined

TABLE I
DATA ON FIVE PATIENTS WITH SICKLE CELL ANEMIA

Case	Age (yr.)	Sex	Race	Weight (lb.)	Study Period No.	Baseline Values				Transfusion Data		
						Hemo-globin (Gm.)	RBC (mil.)	Reticu-locytes (%)	Bilirubin (mg. %)	Amount Blood Given (cc.)	Length of Trans-fusion Period (days)	Days in Hos-pital
1. L. H.	19	M	C	67	1	6.7-7.2	1.9-2.1	29	2.5-3.2	2500	10	27
2. E. H.	18	M	C	74	1	4.8-5.0	1.3-1.7	25	3.1-4.5	2500	6	25
	19	M	C	85	2	5.8-6.0	1.4-2.0	30	6.0	2500	6	16
3. F. G.	10	M	C	71	1	7.2-7.6	2.6-2.8	20	2.3-3.5	1950	9	17
	11	M	C	70	2	6.8-7.3	2.5-2.8	20	3.3-4.4	2500	10	17
4. E. J.	1.5	M	C	20	1	6.6-7.1	2.7-2.8	7	1.1	510	5	19
5. S. H. *	3	F	C	26	1	3.3	1.5	14	1.3	1150 packed rbc.	9	11

* This patient admitted in sickle cell crisis.

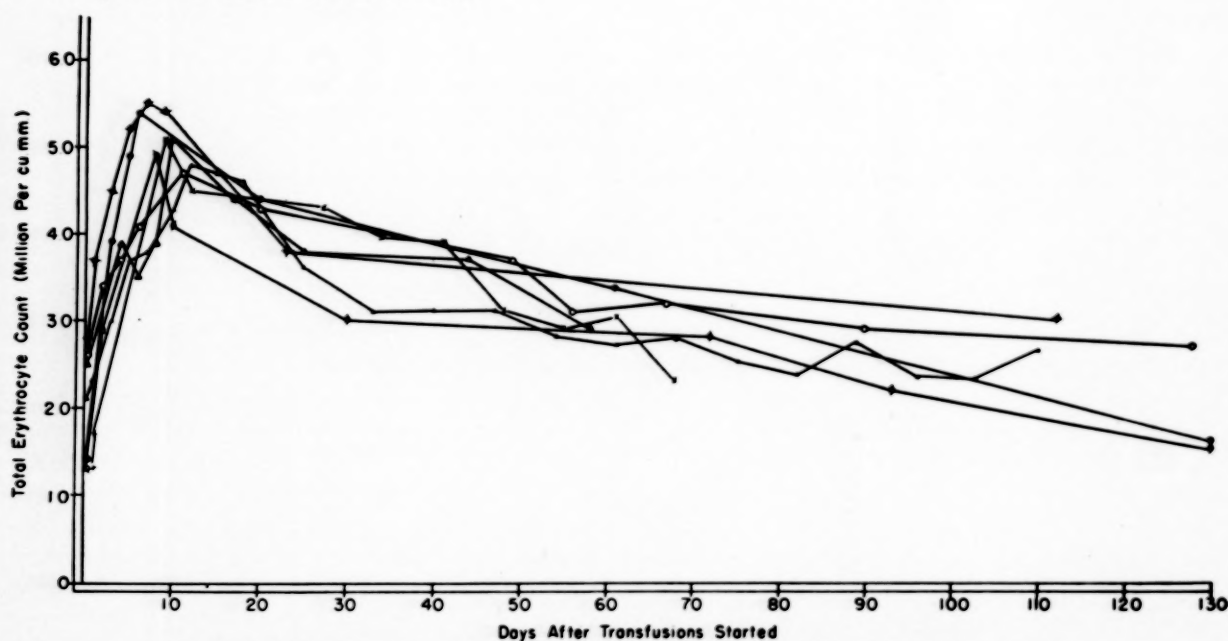


FIG. 1. The effect of transfusions on the erythrocyte count in sickle cell anemia.

5.0 million per cu. mm. was reached within a period of seven to eleven days after transfusions were started. The amounts of whole blood that were administered ranged from 500 cc. given to

at a more rapid rate during the fifteen days immediately after transfusions than in the later period. In most patients the counts reached the level of 3.5 million per cu. mm. within a period

of thirty to fifty days but did not return to the pretransfusion range until about eighty to one hundred days. In several patients the erythrocyte count remained slightly above the pretransfusion level for longer than four months but the differences probably were not significant.

cu. mm. The rise toward the pretransfusion value began between the thirtieth and thirty-fifth day in the patients whose sickle cell counts were followed that long.

Observations made on the plasma bilirubin are shown in Figure 4. Bilirubin levels declined

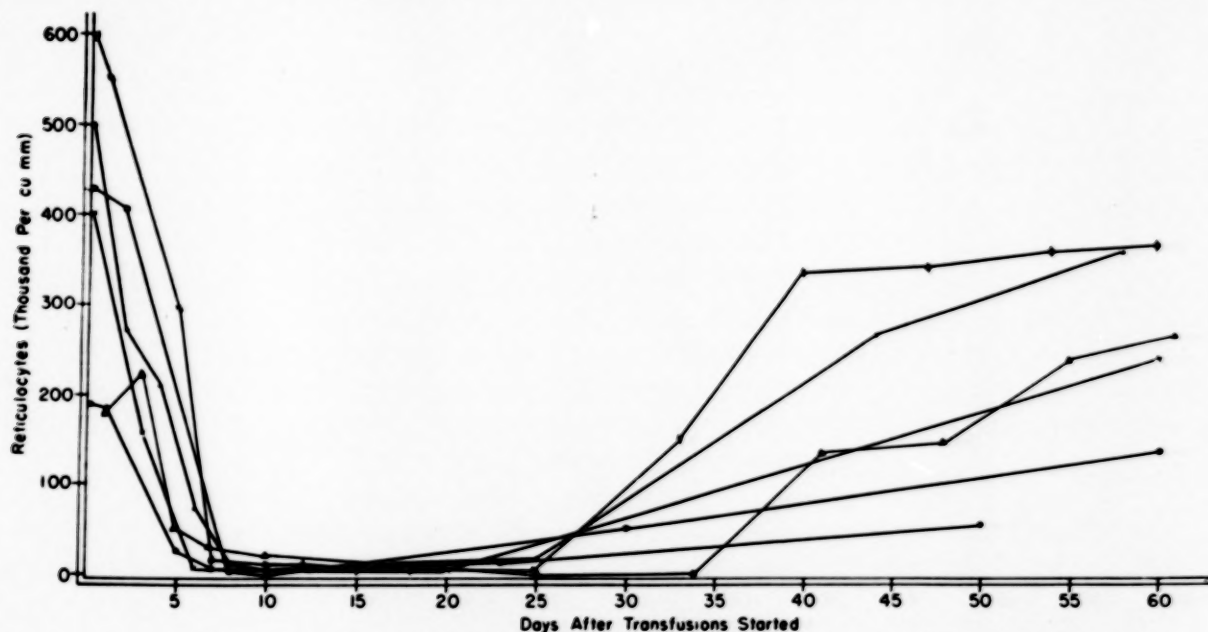


FIG. 2. The effect of transfusions on the reticulocyte count in sickle cell anemia.

The initial reticulocyte counts varied from 200,000 per cu. mm. to 600,000 per cu. mm. (7.0 per cent to 30.0 per cent). The effects of transfusions are shown in Figure 2. Within forty-eight hours after the first transfusion at which time the erythrocyte counts were around 3.0 million per cu. mm., a fall in reticulocytes was apparent. Values of 5,000 to 10,000 per cu. mm. (0.1–0.2 per cent) were reached in from six to eight days. The counts remained in this range for about two weeks. Between the twenty-fifth and thirty-fifth day, when the erythrocyte count again was in the neighborhood of 3.5 to 4.0 million per cu. mm., a rise in reticulocytes became evident.

The changes that occurred in the sickle cell population of the peripheral blood are shown in Figure 3. A decrease soon became evident and by the seventh day it was marked. The decline continued for a period that varied from twelve to twenty-five days in different patients. At the time of the maximum effect the composition of the peripheral blood had altered so that the sickle cells had decreased from about 100 per cent to about 5 per cent, a change from 1.4 to 2.7 million per cu. mm. to 0.1 to 0.3 million per

gradually from the initial range of 1.2 to 4.1 mg. per cent and reached the lowest values between the twelfth and twenty-fifth days at which time determinations varied from 0.5 mg. per cent to 1.5 mg. per cent in different patients. In most patients the plasma bilirubin level began to rise between the twentieth and fortieth days and reached the pretransfusion range in about sixty to ninety days.

The results of four fecal urobilinogen studies which were made on three patients are shown in Figure 5. Satisfactory collections were not obtained in two patients. The excretion decreased in every instance while the patient was in the hospital. The observed decrease in daily fecal urobilinogen excretion is impressive since it occurred despite the increase in the total erythrocyte count and the added load due to the early destruction of some of the transfused cells. One patient was studied on two different occasions and the results were very similar. Attempts to obtain reliable four-day stool collections after the patients had left the hospital were uniformly unsuccessful. Since the lowest sickle cell values and the lowest bilirubin levels occurred after discharge from the hospital, it is probable that

no determinations were made at the time of the lowest fecal urobilinogen excretion.

In two subjects the blood volumes were determined by the Evans blue dye method⁷ before transfusions were started and again several days after transfusions were completed. As compared

COMMENT

In the present study the earliest noticeable effect of multiple transfusions was a decrease in reticulocytes which became apparent within forty-eight hours after the first transfusion. Although normal erythrocyte levels were not

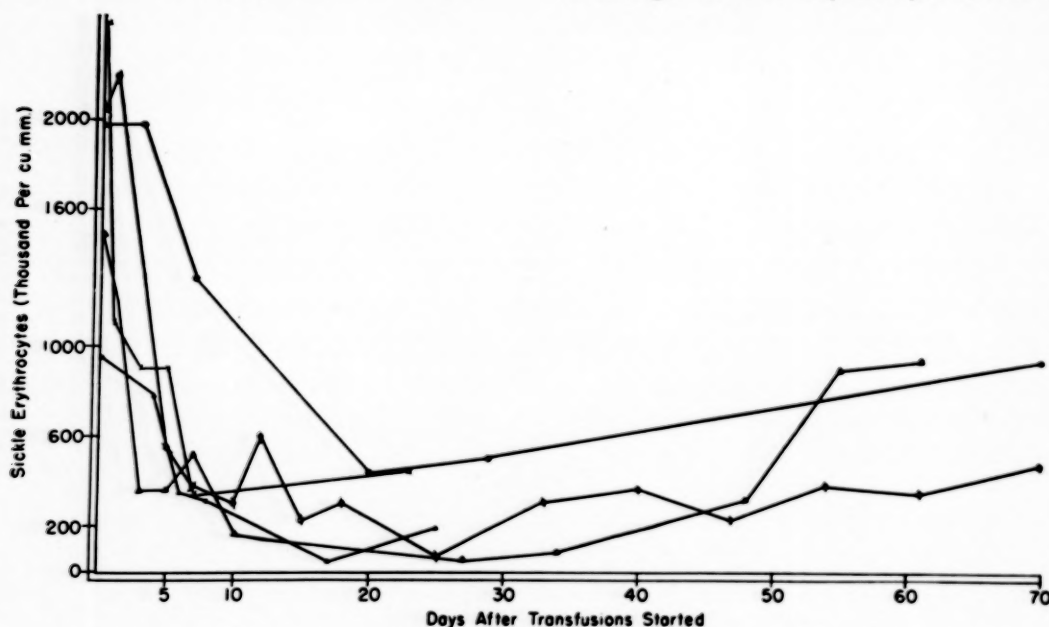


FIG. 3. The effect of transfusions on the number of circulating sickle erythrocytes in sickle cell anemia.

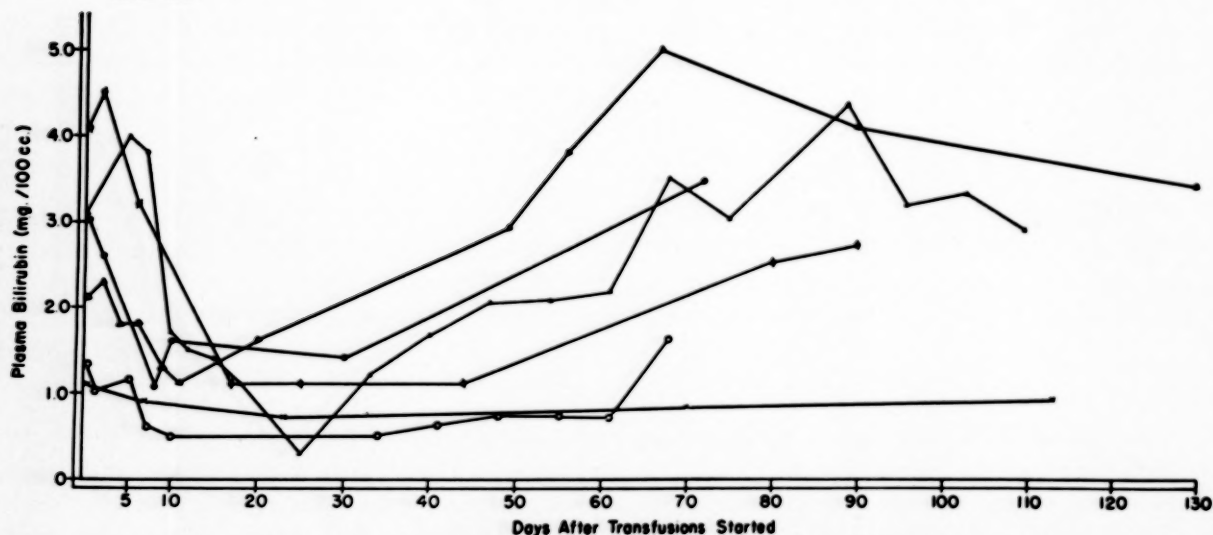


FIG. 4. The effect of transfusions on the plasma bilirubin in sickle cell anemia.

to the expected value for a normal individual of the same size and sex,⁸ the plasma volume was normal prior to transfusion while the red cell volume was about 25 per cent of normal. After the erythrocyte count had been brought to the normal range by transfusions, both the total red cell volume and the total blood volume were in the expected range.

attained until seven to eleven days after the first transfusion, the reticulocyte count reached normal within six to eight days in every instance. Coincident with the fall of reticulocytes there was a prompt reduction in the number of sickle cells in the peripheral blood. In all patients this reduction was marked by the end of the first week and progressed until a time that varied

between the twelfth and twenty-fifth day in different individuals. At this time a striking change had occurred in the composition of the erythrocyte population. Sick cells had decreased from about 100 per cent to about 5 per cent, a change which represented a decline in absolute

the original number remained. Since fewer of these abnormal cells were available for destruction, plasma bilirubin and fecal urobilinogen values declined. Later, when a sufficient number of the transfused normal erythrocytes had been destroyed and the erythrocyte count had fallen

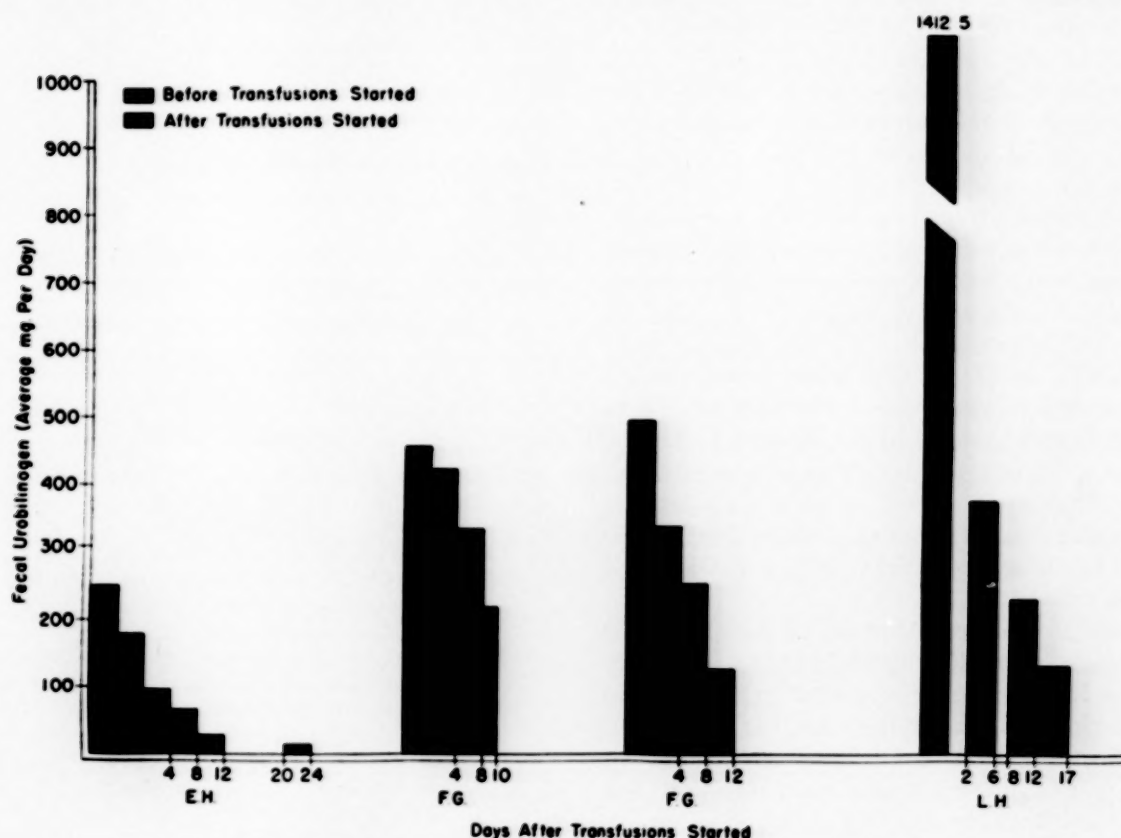


FIG. 5. The changes observed in the fecal urobilinogen excretion following transfusions.

numbers from a range of 1.4 to 2.7 million per cu. mm. to values that ranged from 0.1 to 0.3 million per cu. mm. Plasma bilirubin levels diminished appreciably by the sixth day and reached the lowest levels within twelve to twenty-five days. After approximately twenty-five to thirty days when the erythrocytes had fallen to about 3.5 to 4.0 million per cu. mm., increases in reticulocytes, sickled erythrocytes and plasma bilirubin became apparent.

These observations are interpreted in the following manner: when the anemia was corrected by the use of multiple transfusions, erythropoiesis was depressed and the production of reticulocytes and sickled erythrocytes was reduced. Because of the short life span of the sickled erythrocytes,^{8,9} the number of these abnormal cells in the circulation decreased rapidly. At the end of two or three weeks only a fraction of

to about 3.5 to 4.0 million per cu. mm., erythropoiesis again became active and an increase in reticulocytes and sickled cells occurred. An increase in red cell destruction became apparent at about the same time. As would be expected, the production of a normal erythrocyte count in these subjects did not abolish erythropoiesis entirely. The marrow remained active, sickle cells were never absent from the blood, and serum bilirubin and fecal urobilinogen values remained somewhat elevated in most of the patients.

The changes that were observed in the erythrocytes, sickled erythrocytes, reticulocytes and fecal urobilinogen in this study are similar to those previously reported in single patients by Duane and Evans¹ and ourselves.² Diminished fecal urobilinogen excretion has been noted after transfusion of whole blood by Josephs¹⁰ and after

the administration of plasma by Josephs¹⁰ and Kaplan and Lewis.¹¹ The reason for the changes that they observed after the administration of plasma is not clear.

The risk of anesthesia and surgery in sickle cell anemia has been emphasized by Campbell,¹³ Pratt-Thomas and Switzer¹⁴ and Crastnopol and Stewart.¹⁵ Several reviews of the published reports on the association of pregnancy and sickle cell anemia have revealed a very unfavorable outlook for both mother and child.^{16,17} The complications most frequently observed have been vascular accidents (cerebral, pulmonary, pelvic), infections (pyelitis, pneumonia, puerperal sepsis) and heart failure. The studies of Diggs and Ching,¹⁸ Kimmelstiel,¹⁹ Harris²⁰ and others indicate that many of the clinical features of sickle cell anemia result not only from the anemia *per se* but also from thrombosis or ischemic infarction without thrombosis. These lesions, which may occur in almost any organ, are thought to be due to stasis and congestion in the capillaries or other parts of the vascular system that result from the distortion of the sickled erythrocytes under conditions of lowered oxygen tension.

According to these concepts of the pathologic physiology, correction of the anemia and a reduction in the number of sickled erythrocytes in the peripheral circulation might lessen the complications that have been noted in this disease. The present study indicates that this can be accomplished within a period of one to two weeks by means of transfusions of whole blood or packed erythrocytes. Although no adverse effects were noted in our patients despite the relatively large volumes of blood that were administered within a rather short period, the use of packed erythrocytes would seem more desirable, particularly during pregnancy or in the presence of heart failure. Since the effects of transfusions are temporary, an attempt to keep the level of the peripheral blood within the normal range over a period of many years may be inadvisable because of the likelihood of transfusion hemosiderosis. It is possible that with a low iron intake the risk of hemochromatosis from repeated transfusions is no greater than the risk encountered in the natural course of the disease in children who have a severe form of the disease. Observations over a period of years is necessary to determine this point. Such a study has been initiated in several children under our care.

SUMMARY AND CONCLUSIONS

1. The hematologic changes that were observed in five patients with sickle cell anemia following the production of normal erythrocyte counts by means of multiple blood transfusions are reported.

2. Both hemolysis and erythropoiesis were depressed. During the period of the maximum effect, from the twelfth to the twenty-fifth day, the composition of the peripheral blood was altered markedly. Sickled erythrocytes decreased from the pretransfusion range of 1.5 to 2.5 million per cu. mm. to a range of 0.1 to 0.3 million per cu. mm. The percentage of these cells in the circulating blood decreased from about 100 per cent to about 5 per cent.

3. The possible benefits of multiple transfusions in certain circumstances such as pregnancy and elective surgery are discussed.

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Untoward Hematologic Responses to the Antithyroid Compounds*

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IN the first report of the favorable influence of thiourea and thiouracil upon the course of human thyrotoxicosis attention was called to the occasional appearance of a toxic action upon the bone marrow, as evidenced by agranulocytosis.¹ Every "antithyroid compound" thus far employed therapeutically in the control of the thyrotoxic state has proven capable in some dose of producing a similar although not necessarily as severe depression of certain functions of the bone marrow.

In the peripheral blood reflection of altered bone marrow activity is seen in the mild secondary anemia sometimes produced and the leukopenia with or without granulocytopenia, occasionally progressing to agranulocytosis.² No exhaustive study has been made of the bone marrow, either in laboratory animals or in human beings dying of granulocytopenia secondary to the administration of an antithyroid compound. However, it has been reported that there is a decrease in the myeloid:erythroid ratio of the bone marrow of rats intoxicated with thiouracil.³ In patients intoxicated with an antithyroid compound the sternal marrow has shown a failure in the maturation of the granulocytic series of white cells.⁴ Unfortunately, there appears to be no regularly occurring change during antithyroid compound therapy, either in the peripheral blood or in the bone marrow, by which the appearance of severe depression of bone marrow activity can be predicted.⁵

There is a similar lack of knowledge regarding the mode of action of antithyroid compounds upon the blood-forming organs. Enzyme systems are no doubt poisoned by the drug but just which these are and to what extent they are affected is not clear. The activity of marrow

oxidase may^{6,7} or may not⁸ be inhibited. The tissue concentration of the antithyroid compounds may play an important role, for Williams and his associates⁹ have shown that the concentration of thiouracil in the bone marrow builds up slowly but eventually exceeds that which is attained in the thyroid gland. Such a premise is supported by the fact that granulocytopenic reactions rarely appear before the tenth day of treatment and increase in frequency the larger the dose of the antithyroid compound used. However, such a large percentage of patients completely escapes these effects, even with long-continued administration of an antithyroid compound,^{10,11} that it seems necessary to recognize some constitutional inferiority or susceptibility as also playing a role.

For all practical purposes granulocytopenia or agranulocytosis is the one bone marrow reaction with which the physician is concerned. In man derivatives of aniline, thiourea, thiazole, thiobarbituric acid, thiouracil and thioimidazole have been employed for their possible influence upon thyrotoxicosis. When therapeutic indices are considered, i.e., effectiveness as compared with the incidence of toxicity, it has been found that none of the aniline, thiobarbituric acid or thiazole compounds is clinically useful in the control of this condition. After extensive use the same conclusion seems to have been reached by most authorities in regard to the use of thiourea and 2-thiouracil. Severe granulocytopenia and fatal agranulocytosis have occurred all too frequently in connection with the administration of thiobarbital, aminothiazole, thiouracil and thiourea. (Table 1.) The incidence of severe reactions rises rapidly when excessive doses are employed. For instance, in the case of

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methylthiouracil an incidence of approximately 2 per cent fatality is recorded in the earlier reports. However, the doses used daily were as high as 2.0 gm., as compared with an effective dose of 0.5 gm. (Table I.) Sporadic instances of severe granulocytopenic or agranulocytic reactions have been reported in connection with the use of each of the other effective antithyroid compounds.

In Table I the toxicity of several compounds is compared. This table has been compiled from the sources referred to previously⁴ except for thiouracil, the figures for which are taken from the report of the Council of Pharmacy and Chemistry of the American Medical Association,¹² and for methimazole which summarizes our own as well as the data from the literature.^{11,13-31}

While variations in the individual reports, and the isolated recording of toxic cases without comment upon other observations introduce some errors into the final values, nevertheless from Table I we can gain a satisfactory concept of the relative toxicity of the preparations and of the incidence of the most severe type of toxic reaction observed—granulocytopenia. From this table it is clear that aminothiazole, thiourea, thiobarbital and thiouracil are too toxic for routine use, particularly in view of the fact that much less toxic and more potent materials are available. In effective dosages the other three compounds, methylthiouracil, propylthiouracil and methimazole (tapazole®), are about equally toxic.

Because of its relatively low goitrogenic action in rats, methylthiouracil when first used was administered in much too large doses. The lower row of figures under this drug in Table I shows the high toxicity obtained under these conditions, and is the reason that the use of methylthiouracil did not become popular in this country. Even now it is used rarely, if at all, by most physicians.

The rather low toxicity ascribed to propylthiouracil when first tried clinically was due to the fact that the doses originally employed were much too low to be rapidly effective in the average case of hyperthyroidism. With these smaller doses (0.1 to 0.15 gm. daily) granulocytopenic reactions appeared in but 0.1 per cent of all cases and no fatalities occurred. However, since effective doses have been used the incidence of granulocytopenia has risen to 0.3 per cent and mortality to 0.1 per cent. (Table I.)

In the first patients whom we treated with

methimazole (Table I) there was not a single toxic reaction, for the maximum daily dose was 25 mg. However, some patients failed to respond to such doses¹¹ and subsequently larger doses have been employed. From these, the cases in the literature¹³⁻³⁰ and two personal

TABLE I
TOXIC REACTIONS TO SEVERAL ANTITHYROID COMPOUNDS*

Drug	No. of Patients (approx.)	Daily dose of Drug (gm.)	Total Toxicity (%)	Granulocytopenic Reactions (Total %)	
				Total	Fatal
Aminothiazole...	187	0.4 - 0.8	30.2	2.12	0.65
Thiourea.....	200	1.0 - 2.0	15.0	0.50	0.10
	175	2.0 - 5.0	35.0	4.00	1.50
Thiobarbital....	30	0.1 - 0.2	25.0	3.00	3.00
	28	0.2 - 0.4	28.5	10.80	3.00
Thiouracil.....	5,745	0.4 - 1.0	13.1	2.50	0.40
Methylthiouracil.	268	0.3 - 0.6	3.7	0.30	0.00
	120	0.6 - 1.4	26.8	3.00	2.00
Propylthiouracil.	931	0.1 - 0.15	2.8	0.1	0.00
		0.25 - 0.50	4.5	0.3	0.10
Methimazole.....	60	0.015 - 0.025	0.0	0.0	0.0
	900	0.03 - 0.06	5.4	1.00	0.1

* These data are derived from reports summarized in Reference 4, the report on thiouracil by the A.M.A. Council on Pharmacy and Chemistry,¹² and all cases known to have received methimazole.^{11,13-32}

communications^{32,33} it would appear that the over-all incidence of toxic reactions to methimazole is between 5 and 6 per cent and the percentage of granulocytopenic reactions about 1.00 per cent with but one fatality³⁰ reported thus far. Therefore, it is evident from a review of Table I that methylthiouracil, propylthiouracil and methimazole are about equally toxic in correspondingly effective doses and that instances of bone marrow depression will probably be seen with equal frequency in using these three drugs.

In Table I it can be noted that granulocytopenia was present in 1.00 per cent of the patients taking methimazole in the larger doses, as compared with 0.3 per cent for each of the other two drugs in effective dosage. In fairness to this newer and still less extensively employed drug this statement needs further clarification. It can be noted from Table II that in three of the six reports of granulocytopenia appearing in the literature the authors have been concerned solely with the important task of calling attention to and recording the toxic reaction. Two of our three patients were referred to the hospital only for the management of the toxic reaction and actually represent cases from the series of other observers. Irwin, Van Vactor and Norris'

case²⁸ has been omitted from this table, as in retrospect it was believed by the authors not to have been a toxic reaction.³³ It seems, therefore, that any true value for the incidence of granulocytopenia or agranulocytosis due to methimazole will be lower than that recorded in Table I. The important point is that, somewhat

contrary to earlier reports, toxicity can and does occur and precautions should be taken by every clinician to guard against it.

We now use methimazole initially in a daily dose of 30 mg. We increase the dose only in the patients who do not begin to respond to such a dose within a week. This means that not more

TABLE II
GRANULOCYTOPENIC REACTIONS ASSOCIATED WITH THE ADMINISTRATION OF METHIMAZOLE*

Investigator	Total Cases Reported	Lowest		Dose of Drug (mg.)		No. of Days Drug Administered	Comment
		W.B.C. (cu. mm.)	Poly-morpho-nuclears (%)	Daily	Total		
Bartels ^{18,31,32}	214	4,650	12	20	360	18	Asymptomatic reaction; drug was started immediately following recovery from a severe agranulocytic reaction to propylthiouracil
Bartels ³²	1	4,450	0	15 50 60	315 700 360	41	"A true case of agranulocytosis"; 8 days without any polymorphonuclear cells in peripheral blood; 18 days for blood count to return to normal
Croke and Berry ²³	1	1,900	0	60	1,020	17	Onset with chills, diarrhea and fever; count noted appeared on the second day of reaction; granulocytes reappeared on the fourth day
Specht and Boehme ³⁹	1	1,300	0	30	1,020	34	Patient showed symptoms 5 days before drug was stopped; died 18 hours after admission to the hospital with high fever and jaundice
Stone et al. ²⁵	21	2,600	23	60	600	10	Had been "hypersensitive" to administration of propylthiouracil for 3 days; febrile reaction with each of 4 attempts to use methimazole
Stone et al. ²⁵	21	5,000	23	60	600	10	Thrombocytopenic purpura (41,000 platelets per cc.) developed
McGavack and Chevalley ¹¹ . . .	184	700	8	60	1,500	35	Febrile reactions with fever to 102.4°F.; count noted was on sixth day; recovery by eleventh day
McGavack and Chevalley ¹¹ . . .	184	1,400	10	40	2,240	56	Febrile with highest temperature 102.0°F.; count noted was on seventh day; recovery by twelfth day
McGavack and Chevalley ¹¹ . . .	184	2,800	20	30	1,260	42	Highest temperature 100.2°F.; count noted on fourth day; recovery by eighth day

* Irwin, Van Vactor and Norris' case²⁸ has been omitted from the table as in retrospect it proved not to be a reaction to methimazole.³³

than 25 per cent of the patients receive a large dose. Of these, approximately four-fifths require a maximum dose of 40 mg. daily, while the remainder (5 per cent of the total) will need more. It can be seen in Table II that the higher the dose and the longer the higher dose is continued, the greater the incidence of granulocytopenia. For these reasons we believe a dose of 40 mg. should be exceeded only if three weeks of trial fail to bring about considerable improvement. Furthermore, if larger doses are required they should be diminished at the first sign of improvement. In this way we have come to believe that the reactions to methimazole can be decreased to a fraction of 1 per cent.

There is a further difference between the bone marrow intoxications caused by methimazole and those due to the thiouracils. In the case of the latter two, when the white blood count has dropped below 3,000 per cu. mm. with a simultaneous fall of the polymorphonuclear cells to 30 per cent or below, the reaction almost invariably has proceeded to complete agranulocytosis. Of the nine recorded instances of granulocytopenia noted in Table I, initial counts in seven following the onset of symptoms were below the levels mentioned, but only in three did the granulocytes disappear entirely.

In summary, it appears that the bone marrow reaction to antithyroid compounds is a truly toxic rather than an allergic one, in which the nature of the drug, the size of the daily dose, the duration of administration and a susceptible constitution all play a role. None of the effective drugs used thus far is wholly free of such toxic activity, although in three of them this is so low that clinical usage, with proper precautions, is justified.

Rules for avoiding granulocytopenic reactions are simple and usually helpful: (1) Use the average effective dose of the compound to be employed; increase this only when the initial dose has failed to improve the patient. (2) If a larger than average dose of compound is employed, decrease this as soon as improvement begins. (3) If the average effective dose is satisfactory, continue this dose until the patient is euthyroid and then decrease, at first rapidly and then gradually. (4) Have the patient report to the physician if and when he has a sore throat, an unexplained fever, generalized aching, a rash or generalized pruritus. (5) Check the blood count immediately in the patient with active symptoms. If leukopenia of severe degree is

present (less than 2,500 cells with a normal differential count or less than 3,000 cells with a diminished percentage of granulocytes), stop the drug at once, give penicillin and an abundance of fluids. Various liver and vitamin preparations have been suggested as part of the therapeutic regimen. Despite some favorable laboratory studies on small animals, we have yet to see any unequivocal proof that any of these agents influence the course of agranulocytosis due to antithyroid compounds as it appears in the human being. Transfusions may actually do harm.

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Hereditary Hemorrhagic Telangiectasia*

Nine Cases in One Negro Family, with Special Reference to Hepatic Lesions

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HEREDITARY hemorrhagic telangiectasia is a well known disease, as evidenced by the fact that 1,451 cases were reported¹ to 1950, yet certain aspects of the syndrome remain to be clarified. One of these is the fact that of all the recorded cases only two isolated instances have been noted in the Negro race.^{2,3} Another is the controversy which has existed as to whether or not hepatic lesions occur in this disease and, if so, the nature of such lesions. Occurrence of the disease without visible telangiectasia has also been debated, although such cases have been recorded previously on several occasions.^{4a,b}

We have recently studied nine cases in one Negro family, an opportunity which arose as the result of investigation of recurrent severe epistaxis, without apparent telangiectasia, in a thirteen year old colored boy. Enlargement of the liver in this boy had been noted throughout sixteen hospital admissions in the preceding eight years. We found that while no cutaneous lesions were demonstrable in this family, venous telangiectases were present on nasopharyngoscopic examination in all nine available members of the immediate family. Hematologic studies of this family revealed thrombocytomegaly with moderate thrombocytopenia in the four most severely affected members, these findings being absent in the rest. Deafness of moderate to severe degree was present in four members of this family. In a review of the available literature, we have found that neither of the latter two factors has been investigated in this disease. For these reasons we present the following cases, along with the histologic findings in the first such case in which liver biopsy was performed. In addition, the autopsy findings of

liver involvement in a seventy-one year old white female with this disease are recorded.

PRESENTATION OF CASES

The first patient (L. B. No. 239517), a thirteen year old Negro boy, was born by normal spontaneous delivery in Grady Memorial Hospital on November 22, 1940. He was not seen again until 1945, except for outpatient therapy for purulent otitis media at the age of ten months. Since 1945 he has been admitted sixteen times, with an average of twenty-seven days each admission, for a total of 432 hospital days.

On July 9, 1945, the then five year old child entered because of spontaneous attacks of epistaxis which had occurred during his first year. His mother stated that he had developed fairly normally up to one year of life, when he was noted to be lethargic, weak and susceptible to nose bleeds at the slightest provocation. These seemed to be seasonal in occurrence, more marked in hot weather, and lasted from thirty minutes to four or five hours. He had always been retiring in nature and appeared less strong than the other children. There was no history of hematemesis, melena, hemoptysis or purpura.

Positive physical findings in 1945 included a low grade fever, tachycardia, icteric sclerae and evidence of recent hemorrhage from the right naris. The liver was palpated three finger-breadths below the right costal margin, with a firm edge which was neither nodular nor tender. The spleen was not palpable. Laboratory data are included in Table 1; all tests for a hemorrhagic diathesis were negative at that time. He received four whole blood transfusions (type II, A); while receiving the third a febrile reac-

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tion occurred, the others being uneventful. He was given blood, iron and crude liver extract. His hospital stay was remarkable only for the passage of dark red blood in his stools on several occasions. He was discharged on September 1, 1945, with the diagnosis of epistaxis of undetermined origin.

taken. Upon review of these sections (Fig. 1), the diagnosis of post-hepatic cirrhosis was reconfirmed. This is the first reported instance of liver biopsy in this disease. The intractable nosebleeds continued relentlessly until on January 28, 1950, during his twelfth admission, a right external carotid artery ligation was done,

TABLE I
LABORATORY DATA*

Date	R.B.C. (millions)	Hgb. (gm.)	Hct.	Platelets	Total Protein (gm. %)	Cephalin Flocculation Test	Thymol Turbidity	Icteric Index	Comments
7- 9-45	3.23	6.0	16	171,000	7.2	1+	11
8- 1-45	4.29	13.0	5.1	neg.	Alk. phosphatase 1.3 B.U.
5- 1-46	1.23	1.6	5.7	3+	No significant response to folic acid therapy
7-23-47	2.00	2.6	10	6.7	neg.	5 units	16	X-ray: "cardiac enlargement and splenomegaly"
2-23-48	4.08	10.2	7.4	1+	5 units	28	"No roentgenologic evidence of esophageal varices"
10-27-48	1.28	3.0	10.5	6.7	neg.	15 units	11	Cellular bone marrow, negative skull films
4-26-49	0.85	2.9	"Marked cardiac enlargement; lungs show only mod. cong."
11-29-49	2.20	3.8	15	170,000	7.4	1+	8 units	8	1st PPD: neg., Kahn: neg., histoplasmin: neg.
1-27-50	4.00	8.5	neg.	20 units	..	EKG: "Lt. ventric. hypertrophy"
11-17-50	2.86	3.2	9	114,200	"Essent. normal bone marrow"
5-13-52	2.13	4.1	1+	24 units
12- 8-52	1.93	3.0	13	90,000	6.8 (alb: 3.0 glob: 3.8)	1+	12 units	..	BSP: 20% retention in 45 min.
2-13-53	3.11	8.8	27	139,490	6.6 (alb: 3.0 glob: 3.6)	3+	5 units	..	Serum bilirubin: 0.4 mg. %; stool guaiac-neg.
4-10-53	3.37	6.4	24	136,000 (large platelets)

* Urine, bleeding time, coagulation time, clot retraction time, erythrocyte fragility, prothrombin time repeatedly normal. Sickling, negative; gastrointestinal series: negative for esophageal varices; reticulocytes: 0.6 % to 17.7 % (average: 3%).

All subsequent admissions were because of extreme anemia due to intractable epistaxes, and he frequently entered with hemoglobin levels ranging from 1.6 to 3 gm. per cent. Up to the time of this writing he had received over seventy whole blood transfusions of from 300 to 500 cc. each. During his third hospital admission in 1946 jaundice was again noted and his spleen was palpated for the first time. Since then splenomegaly has been persistent. On his fourth admission in 1947 cardiomegaly with tachycardia and a systolic gallop rhythm with both systolic and diastolic basal murmurs were noted. Hepatic and splenic enlargement were again manifest and extramedullary hematopoiesis was suspected as the cause. Hemorrhagic telangiectasia was mentioned in the differential diagnosis at that time but never received much consideration because there were no visible telangiectases. Because of the clinical suspicion of "Banti's syndrome," liver biopsy was under-

since all local measures had proved unsuccessful. However, this procedure also proved unavailing.

One of us (J. L. S.) first encountered the patient when he was transferred from the pediatric to the medical service. Other than the epistaxes, no bleeding or bruising tendency had been noted. Family history at that time revealed that although all of his siblings had had epistaxes, in only his mother, two brothers and one sister were these severe enough for visits to the hospital.

Physical examination on December 2, 1952, revealed blood pressure 120/0 mm. Hg, temperature 100°F., and weight 50 pounds. He was an underdeveloped twelve year old boy presenting marked pallor of the skin and mucous membranes. Positive findings included a low grade fever, slight pallor of the optic discs and marked cardiomegaly with a forceful apical impulse visible at the left anterior axillary line. A grade III systolic murmur was heard diffusely over the precordium, loudest in the left second and



FIG. 1. Liver biopsy revealing post-hepatic cirrhosis.

third interspaces. The upper border of the liver percussed in the fifth right interspace in the mid-clavicular line; the tender lower border was palpable 4 cm. below the costal margin and extended to the left of the midline in the epigastrium. The spleen presented a round, smooth, firm edge 3 cm. below the costal margin. Soft, generalized, discrete lymphadenopathy was noted. An anterior nasal septal perforation testified to the frequent cauterizations. No telangiectases were visible on the skin or mucous membranes. There was no jaundice, fetor hepaticus or palmar erythema.

In the hospital severe epistaxis, requiring eight transfusions of type A blood and anterior and posterior nasal packing, occurred in the first four days. Cauterization of a local bleeding point superior to the perforation decreased the epistaxis. Further transfusions, ferrous sulfate and a high protein diet were administered. There was a rapid decrease in cardiac dilatation and hepatomegaly, the liver receding to the former level of 4 cm. below the right costal margin. He was discharged improved on December 23, 1952.

Findings in Family. This patient's mother, age forty-two; four brothers, ages eleven, twelve, fifteen and sixteen; and three sisters, ages nine, nineteen and twenty-two were then investigated. The father, age fifty-two, and one brother, age twenty-four, were not available. Careful search revealed no cutaneous telangiectasia and no hepatosplenomegaly in any member of the patient's family. After topical anesthetization with two per cent cocaine, nasopharyngoscopy

by one of us (M. I. L.) demonstrated prominent, unmistakable telangiectasia at the posterior end of the middle turbinates, around the torus tubarius bilaterally, and diffusely scattered over the entire posterior nasopharyngeal vault in the patient and in all eight members of his immediate family examined. These lesions were composed of submucous, dilated, tortuous, convoluted vessels consistent with enlarged capillaries or venules. A son of the oldest sister was examined but these lesions were not found in his nasopharynx.

We noted that the mother was totally deaf, and that it was necessary to speak loudly and distinctly to the twelve and fifteen year old brothers. Further questioning revealed that the twenty-four year old brother, who was absent, had worn a hearing aid for several years. Since the nature of this deafness has yet to be determined, it remains to be seen whether it is significant or coincidental. Hematologic studies of this family revealed that thrombocytomegaly and moderate thrombocytopenia (circa 100,000 per cu. mm.) were present in four of the ten, and absent in the others.

COMMENTS

Rendu-Osler's disease has been defined⁵ as a hereditary affection manifesting itself in localized dilatations of capillaries and venules, forming distinct groups or telangiectases, which give rise to profuse hemorrhage either spontaneously or as the result of trauma. The typical history consists of the onset of epistaxis in child-

hood, varying in intensity and frequency, and the development around the ages of twenty to thirty-five of varying morphologic forms of reddish to violaceous cutaneous telangiectases. These lesions usually increase in number as age advances. The diagnostic triad consisting of (1) hereditary tendency, (2) presence of visible telangiectases and (3) tendency to bleed from these lesions, has been emphasized^{6,7} as essential for diagnosis. However, the insistence upon a familial or hereditary history has been modified by Fitz-Hugh's⁸ emphasis of atavism, or "skipped generations." Stock⁹ stated that "it is highly probable that in about 20 per cent of the recorded cases the disease developed in the total absence of a family history of its occurrence." The well known occurrence of epistaxis preceding by many years the development of visible telangiectases is re-emphasized by our cases. Fitz-Hugh⁸ summarized this by stating: "Telangiectases, however, are not discovered as a rule until adult life is reached. For . . . the lesions do not appear on the face and other cutaneous surfaces until after twenty years of age in most instances."

Blumenfeld¹¹ in 1926 and Giffin¹² in 1927 reported a syndrome of familial epistaxis without telangiectasia. This diagnosis was made initially in our first case until nasopharyngoscopy revealed multiple telangiectases. Since neither of these authors mentioned nasopharyngoscopy, this syndrome comes under question, as telangiectases may be lacking on external inspection although abounding in the posterior nasopharynx. It is interesting that five of our nine patients were asymptomatic and never had consulted a physician. They were diagnosed only by investigating the family of our first case. This may explain why this disease can occur in the absence of a positive family history.

Garland and Anning¹ in a complete biographic study stated that 244 recorded families had been reported to 1950, including 648 males and 703 females (sex not stated in 64) for a total of 1,451 affected persons. In 112 families in which full sibships were given, the ratio was 449 males to 463 females. Of 463 individuals who transmitted the defect, 220 were male and 243 female. Thus it is established that the disease, which is transmitted as a mendelian dominant, affects both sexes equally. The racial incidence is of interest. Wintrobe¹⁰ stated that the patients have been of the following stock, in the order named: (1) Anglo-German, (2)

Latin, (3) Scandinavian and (4) Jewish. He mentioned but a single report² in the Negro race and we have found only one additional such instance.³

The differential diagnosis of true familial epistaxis has generally included¹³ three conditions: (1) Hereditary hemorrhagic telangiectasia; (2) pseudohemophilia (von Willebrand's disease)¹⁴ and (3) hereditary familial purpura simplex (of Davis).¹⁵ Although some overlapping of these has been reported,^{16,17} the presence of visible telangiectases, with a typical history, is diagnostic of Rendu-Osler's disease. These patients may bleed from any site of the lesions. Therefore, two other aspects of the disease should be considered: (1) The morphology of the lesions and (2) the sites of their occurrence. Osler^{18,19} described three types of lesions in this disease: elevated or nodular forms, simple arterial spiders and violaceous macular types. The most typical cutaneous lesion is a small (1 to 3 mm.) punctiform, non-elevated, purple telangiectasis. These lesions appear in the following sites in decreasing order of frequency: nasal mucous membrane, inner surface of lips, gingiva, buccal mucosa, palate, tongue, skin of face, trunk, fingers, under the nails, conjunctiva, scalp and ears. Visceral lesions are also frequently encountered in the stomach, respiratory tract, uterus, kidney, bladder, meninges, brain, spinal cord and eye. These lesions may bleed on the slightest trauma or even during sleep, although there is no undue bleeding from cuts of unaffected skin. The number of unusual syndromes presented by this disease is far too great to be included in this discussion which is concerned chiefly with hepatic lesions; hence pulmonary arteriovenous fistulas,²⁰⁻²⁶ which have been the chief concern of authors during the past decade, and other manifestations such as retinal bleeding, associated with Sturge-Weber, Hippel, Lindau, Bourneville's disease, etc.,²⁷ will not be discussed here.

The basic pathologic lesion has caused some controversy, chiefly as to pathogenetic and etiologic significance. There have been four basic schools of thought. The first describes enlarged vessels lined by a single layer of endothelial cells, with no muscular or elastic layer. This histologic description, first given by Hanes,⁵ has been concurred in by the majority of investigators.³⁸⁻⁴⁰ A minor variation was Fingerland and Janousek's⁴¹ belief that the disease represents simply a dilatation of the



FIG. 2. Liver from autopsied case revealing subcapsular telangiectasia.

venous portions of precapillaries. The second group agrees that the small vessels are dilated and elastic fibers are diminished but believes that the primary lesion is a weakness of connective tissue, because of the occurrence of hernias and varicosities in these patients⁴² on occasion, and degeneration of collagen and elastic fibers in areas of skin not affected by telangiectases.⁴³ Ullmann⁴⁴ proposed the third idea, that the lesion is not a dilatation but a new formation of vessels. Finally, Ravina,⁴⁵ quoting Duvoir, Benkö⁴⁶ and Pillsbury^{47a} proposed widespread multiple congenital anomalies as the chief feature, with constitutionally weak capillary endothelium, young vascular tissue,^{47b} or endothelial rests of embryonal origin representing merely the superficial component of a process associated with visceral angiomas.

Autopsied Case of Telangiectasia of the Liver. This seventy-one year old white female had had recurrent bleeding from the nose, mouth and gums for many years, with subsequent anemia, and had received many transfusions during the ten years preceding her death. She had multiple cutaneous and mucous membrane telangiectases. She died in this hospital with coronary and cerebral arteriosclerosis in 1949, and autopsy (No. A-49-406) revealed telangiectasia in skin, gastrointestinal tract and liver. The section of liver reveals multiple subcapsular telangiectasia and chronic hepatic congestion but no evidence of cirrhosis. (Fig. 2.)

These histologic findings agree with the majority of observers, although we draw no pathogenetic conclusions therefrom. Thus the

telangiectasia are simply blood-filled spaces lined by a single layer of endothelium, surrounded by a thin zone of connective tissue lacking in muscular and elastic components. This lack of protection explains why hemorrhage is so easily induced and at times so difficult to control in those delicate lesions located immediately beneath a thin cutis or mucous membrane.

Hepatic Lesions. The subject of hepatic lesions occurring in or concomitant with Rendu-Osler's disease is perhaps the most confused aspect of the syndrome. Opinions have varied as evidenced by the following: Brandel⁴⁸ stated: "Osler pointed out that a certain connection existed between hereditary telangiectasia and liver disease and since then a number of cases of this combination have been recorded. The liver changes generally take the form of cirrhosis, chiefly of Laennec's type." However, Schuster,³⁹ in a review of the nine autopsied cases to 1937, stated: "enlarged livers found clinically in these patients have often been presumed to be cirrhotic, but this has only once been confirmed at autopsy. The ordinary portal cirrhosis of middle life is so often accompanied by telangiectasia that there is a temptation to assume an analogous connection in familial telangiectasia. There is very little clinical or pathological support for this assumption."

Hepatomegaly, which has been noted frequently, has been the subject of a good deal of speculation but very little objective information is available. Hence it is difficult to assess the incidence and severity of the hepatic lesions in those cases reported. In 1931 Fitz-Hugh⁴⁹

presented a case in which, after twenty years of moderately severe epistaxis, splenomegaly developed before age fifty, and hepatomegaly at age fifty-eight, both before the first transfusion. This patient died of acute atrophic toxic hepatitis after the third transfusion. Fitz-Hugh therefore emphasized three unusual features of the disease: (1) Splenomegaly and hepatic enlargement, (2) intolerance to transfusions and (3) the interesting coincidence of identical blood groups ("O," or type IV, Moss). Many cases have since been reported with blood groups "A" and "B" but this matter has not been finally settled, as Vischer⁴³ pointed out that these may represent heterozygous instances. Bean⁵⁰ said in 1945: "Hepatomegaly and splenomegaly have been specifically noted in not more than two per cent of all the cases reported." He regarded hepatic and splenic enlargement as coincident rather than intrinsic findings, and considered hemorrhage into the liver or spleen as possible causes for enlargement in those instances reported. Ashby and Bulerm⁵¹ stated that hepatomegaly had not been noted in any of the fifty-six patients of Garland and Anning.

There is conflicting opinion even concerning the autopsied cases. According to Brandel,⁴⁸ Johnson and Nordenson found some disturbance of liver function in all of eight cases and they stated that in all autopsied cases cirrhosis of the liver was found. For this reason they considered liver damage leading to atypical cirrhosis a feature of the syndrome. However, Schuster³⁹ found that although in life liver enlargement was usually accompanied by splenic enlargement, in four of the five complete postmortems recorded to 1937 the spleen was enlarged but not the liver. In two⁴⁹ there was acute necrosis of the liver following transfusion intolerance, the other two had an indeterminate condition and in Schuster's case congestion and degeneration of the liver attributable to heart failure, with venous dilatation and patchy periportal and peribiliary fibrosis but no generalized fibrosis, was found.

In 1935 van Bogaert and Scherer⁵² reported an autopsied case with both hereditary telangiectasia and Laennec's cirrhosis. This was a forty-six year old male who had been a consumer of alcohol and narcotics since age nineteen. Werner⁵³ autopsied a forty-three year old male and found in the 1,700 gm. liver that the capsule was thickened and that telangiectases were present in connective tissue strands through-

out the section, but stated that "a true cirrhosis is not present."

Hepatic lesions have been noted by many other authors.^{18-20,54-71} Vischer's⁴³ autopsied case revealed slight inflammatory and circulatory changes of the liver with fatty infiltration but no cirrhosis. A fascinating case was reported by A. J. Brink³¹ of a nineteen year old woman with an epigastric hernia of five years' duration. At operation a pulsating hemangiomatous mass extending into the liver along the falciform ligament was found. She also had a pulmonary arteriovenous fistula, telangiectases of skin, palate, etc., and splenomegaly. Her liver function tests revealed prothrombin time, 65 per cent of normal; thymol turbidity, 4 plus; and alkaline phosphatase, 29.6 K-A units. The serum cholesterol, total protein, albumin and globulin were normal. Brink suggested that the splenic enlargement in his case was either associated with the hemolytic tendency⁷² or was due to portal hypertension because of arteriovenous anastomoses in the pulsating hepatic angiomatous mass. Ytrehus⁷³ autopsied a fifty-four year old woman with Rendu-Osler's disease and found cirrhosis, closely resembling Laennec's type, but with telangiectatic dilated vessels in liver, nasal mucosa and brain. He advised extra caution in administering potentially hepatotoxic drugs to patients with telangiectases.

It is therefore evident that hepatomegaly occurs frequently in hereditary hemorrhagic telangiectasia. The etiology of this liver enlargement is difficult to determine from the literature because of conflicting opinions and paucity of objective data. In retrospect, although the frequent occurrence of subcapsular telangiectasia and the reported cavernous hemangiomas of liver in Rendu-Osler's disease would make one wary of biopsy, it has, as in our first reported instance, cast some light upon the cause of hepatomegaly in this disease. It has long been known that hepatomegaly tends to occur in those patients who have manifested the disease for a long time and who have bled severely. Such patients would naturally have received the most blood transfusions. Homologous serum hepatitis and its sequelae are generally considered today as frequent and feared complications of blood transfusion. Patients such as ours, who received seventy transfusions in the past eight years, stand a high statistical chance of contracting this viral disease. Post-hepatic cirrhosis, an entity widely appreciated only in the last few years,

undoubtedly occurred previously in some of these patients but was unrecognized as such. We believe that this should be considered a cause for hepatomegaly in this disease.

Another cause for hepatomegaly is the occurrence of the basic lesion in the liver. This is illustrated by our autopsied case (Fig. 2) and Brink's instance of a cavernous hemangioma of liver presenting as an epigastric hernia.

Still another cause for hepatomegaly in this disease is congestive heart failure secondary to anemia. With hemoglobins ranging from 1.6 to 3 gm. per cent, cardiac decompensation occurred in our patient and the size of his liver increased even further at these times. The acutely swollen, tender liver would promptly resume its former size after adequate transfusion.

Although the biopsy findings of post-hepatic cirrhosis may have been due to hepatitis from multiple transfusions, our patient had icterus and hepatomegaly on his first admission before receiving any blood. Further inquiry revealed that he had received routine parenteral immunizations at two years of age. These could have resulted in homologous serum hepatitis but we cannot exclude the possibility of telangiectasia of the liver in addition to post-hepatic cirrhosis in this patient even though no vascular lesions were seen on liver biopsy.

The occurrence of Laennec's cirrhosis concomitant with Rendu-Osler's disease has been reported.⁵² It seems likely to us that the repeated insults of hepatic anoxia subsequent to severe blood loss, especially in cases as severe as ours, along with protein depletion and dietary inadequacies, would increase any predisposition to Laennec's cirrhosis. Thus the combination of alcoholism (as in van Bogaert and Scherer's case) and nutritional deficiencies might be expected to result in Laennec's cirrhosis in a higher percentage and to a more marked degree in these persons than in normal individuals. However, on the basis of available information we see no more fundamental relationship between Rendu-Osler's disease and Laennec's cirrhosis than this. There was no evidence of cirrhosis in our autopsied case and nothing in the clinical data to suggest Laennec's cirrhosis in our young Negro boy.

Multiple transfusions in our patient raised the question of exogenous hemochromatosis.⁷⁴ Biopsy of a cervical lymph node revealed hemosiderin-laden macrophages in a few fields; however, the absence of such deposits in the liver biopsy, and

the minimal degree seen in this node made such a diagnosis untenable. We have found no such case reported in the literature, as might be predicted since it would be highly unlikely that an excess of iron could be given to patients bleeding frequently and profusely.

SUMMARY AND CONCLUSIONS

1. Nine cases of hereditary hemorrhagic telangiectasia in one Negro family and one additional autopsied case of telangiectasia of the liver are reported. Because of the rarity of reported cases of this disease in the Negro these cases are of unusual interest.

2. The difficulty in diagnosing this disease in infants, in whom epistaxis precedes the development of cutaneous telangiectases, is stressed. The necessity for nasopharyngoscopic examination in such cases is emphasized.

3. Thrombocytomegaly with moderate thrombocytopenia was present in four members of this family but absent in the others. Deafness of moderate to severe degree occurred in four of ten members.

4. Hepatomegaly occurs frequently in hereditary hemorrhagic telangiectasia. It may be due to (1) telangiectases in the liver, (2) post-hepatic cirrhosis, (3) congestive heart failure secondary to anemia and (4) the development of Laennec's cirrhosis upon exposure to alcoholism or nutritional inadequacies.

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Multiple Myeloma Simulating Aplastic Anemia*

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BECAUSE general supportive care is usually the paramount initial concern in aplastic anemia, etiologic considerations are often

marrow aspiration in such cases is often misleading, although the diagnosis in this type of case can be made if a sample of myeloma tumor is

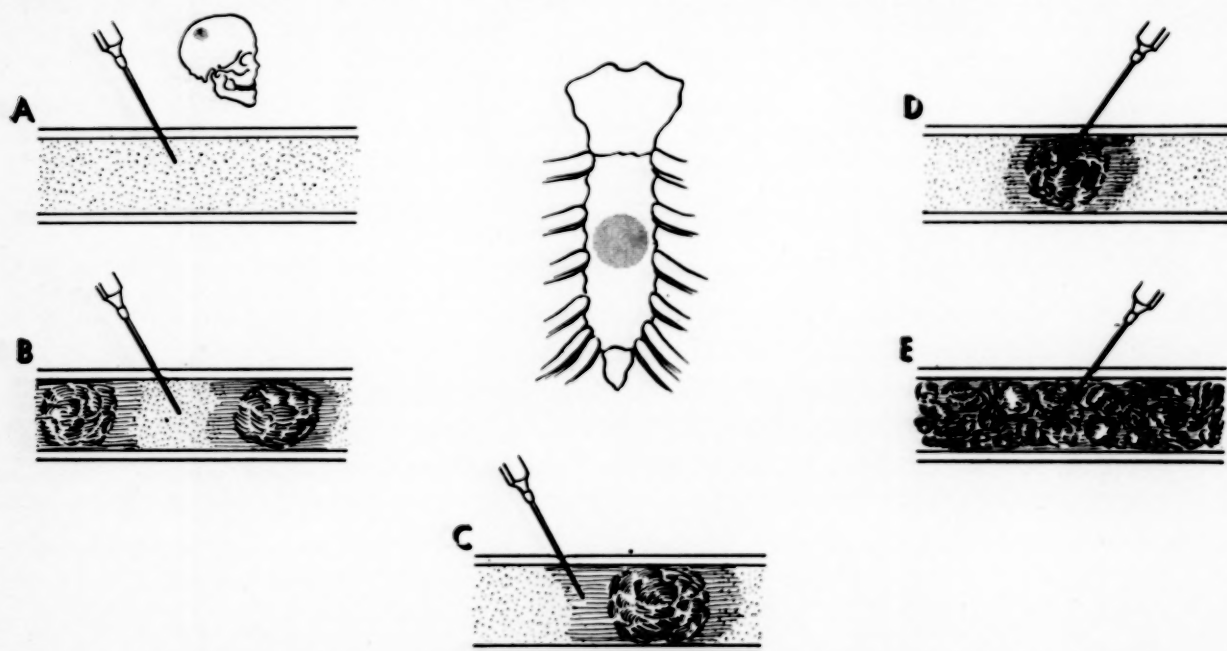


FIG. 1. Marrow aspiration pitfalls in multiple myeloma. A, normal bone marrow aspirate obtained when puncture is made during the very early phase, as in "solitary" myeloma. B, normal bone marrow aspirate obtained during a later phase, when the needle enters between scattered focal lesions. C, non-diagnostic cytology obtained when the aspiration is from the periphery of a focal lesion; an increase in the plasmacytic series but no abnormally immature (myeloma) cells present. D and E, aspiration directly from a tumor nodule or from a marrow diffusely infiltrated presents two possible results: (1) a "dry" tap, due to inability to aspirate a portion of the cohesive tumor, (2) solid sheets of myeloma cells, if the tumor is less cohesive.

deferred and even after study may remain enigmatic. The differential diagnosis seldom includes multiple myeloma. This report presents cases which were nosologically aplastic anemia but etiologically proved to be multiple myeloma.

Multiple myeloma is extremely difficult to diagnose when it is presented as aplastic anemia. Schwartz, Armstrong, Loeffler and Mavrelis¹ state, "Attention is called to the ease with which the condition (multiple myeloma) may be mistaken for aplastic anemia." A negative bone

aspirated. Difficulty in aspiration is not only one of locating the tumor site but sometimes also of removing the dense coherent myeloma tumor. (Fig. 1.)

Although moderate anemia is one of the cardinal findings in multiple myeloma, severe anemia is an uncommon early manifestation.²⁻⁵ The pathogenesis of the anemia is not clearly understood. The three etiologic factors usually considered are listed by Limarzi⁶ and others^{7,8} as follows: (1) tumor replacement of normal

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marrow, (2) metabolic (toxic) inhibition of marrow function by products of myeloma cells and (3) renal failure with consequent azotemia. In addition, Custer⁵ suggests that increased hemolysis is contributory.

In view of the paucity of published reports one would conclude that myeloma is a rare cause of aplastic anemia. In a study of fifty-eight histologically proven cases of myeloma, however, we have encountered three such instances. We believe that myeloma is not as rare a cause of this "symptom" as would at first seem apparent from the literature.

In addition to the case of Schwartz et al.¹ a group of these cases resembling aplastic anemia has been reported by Begemann.⁹ It is considered worth while to report three additional cases for two reasons: (1) report of such cases has been uncommon and (2) for the first time attention has been directed to the incidence of such cases in a review of a large series of myeloma cases. The latter fact serves to emphasize that myeloma should always be included in the etiologic differentiation of pancytopenia.

CASE REPORTS

CASE 1. C. S., a forty-five year old male Negro core room sprayer, was first seen August 26, 1952. He complained of acute right lower abdominal pain, right costovertebral angle pain and hematuria. The patient had been losing weight for over a month and had had back pain for about one week. There was no industrial exposure to toxic agents and he had been taking no medications but had recently partaken of some "corn whiskey."

Blood count on admission revealed a hemoglobin of 9.2 gm., red blood cell count of 3.01 million, white blood cell count of 5,050 with 28 per cent neutrophils, 2 per cent eosinophils, 3 per cent monocytes and 67 per cent lymphocytes. Urine was grossly bloody. Blood non-protein nitrogen was 80 mg. per cent and fasting blood sugar 97 mg. per cent. Erythrocytic sedimentation rate was 25 mm. per hour (Wintrobe; corrected) and the hematocrit 26 mm. Examination of the cerebrospinal fluid revealed a protein of 66 mg. per cent but was not otherwise remarkable. Cephalin cholesterol test was 2 plus with a normal thymol flocculation and turbidity reaction. Prothrombin time was 22 seconds (52 per cent of normal). Blood lead was 9.5 μ g. per cent. Albumin-globulin ratio was 5.1/2.2 gm. per cent. Tests for urinary arsenic and mercury were

negative. Carbon dioxide combining power was 39.6 vol. per cent and the plasma chlorides 563 mg. per cent.

Progress laboratory examinations revealed increasing anemia, a last hemoglobin determination on September 9th being 7.1 gm. Urinalyses revealed 4 plus albuminuria with a specific gravity of 1.014 and decreasing numbers of red blood cells. There were no casts. Non-protein nitrogen progressively increased to 155 mg. per cent.

Blood examination by the special hemocytologic laboratory revealed a platelet count of 36,000 per cu. mm., normocytic red blood cells and marked rouleaux formation. Percentile distribution of the white blood cells was essentially as before, except that on September 3rd the peripheral blood contained 2 per cent plasma cells, 5 per cent proplasmacytes and 5 per cent histiocytes. Sternal marrow aspirations were examined on August 29th and September 5th. The myeloid: erythroid ratio on these examinations was increased from 9.2:1 and 15.6:1. Both erythrocytic and granulocytic series were depressed and the megakaryocytic series was virtually absent. The plasmacytic series was increased to 3.6 per cent and 11.0 per cent but most of these were mature plasma cells. The report was as follows: "There is general hypoplasia but even so, normoblasts and megakaryocytes are disproportionately decreased."

Intravenous pyelograms made on the day of admission revealed the absence of renal function bilaterally. Except for some cardiac enlargement the chest x-ray was normal. Skull x-rays were normal. Spine x-rays revealed advanced degenerative changes and narrowing of the disc space between C-2, 3, 4, 5 and 6. No localized area of bone destruction was noted. The electrocardiogram revealed delayed activation of the left ventricle.

The day after admission the patient became psychotic and during the remainder of the hospitalization required sedation and close observation. Urinary output progressively diminished to less than 400 cc. daily. The temperature remained normal; there was tachycardia, ranging between 100 and 120 beats per minute; the blood pressure receded to 140/70 mm. of Hg where it remained.

Therapy was symptomatic and consisted of tube feeding, sedation and cortisone[®] 100 mg. intramuscularly q.i.d. Antibiotics (penicillin and streptomycin) and British anti-lewisite were

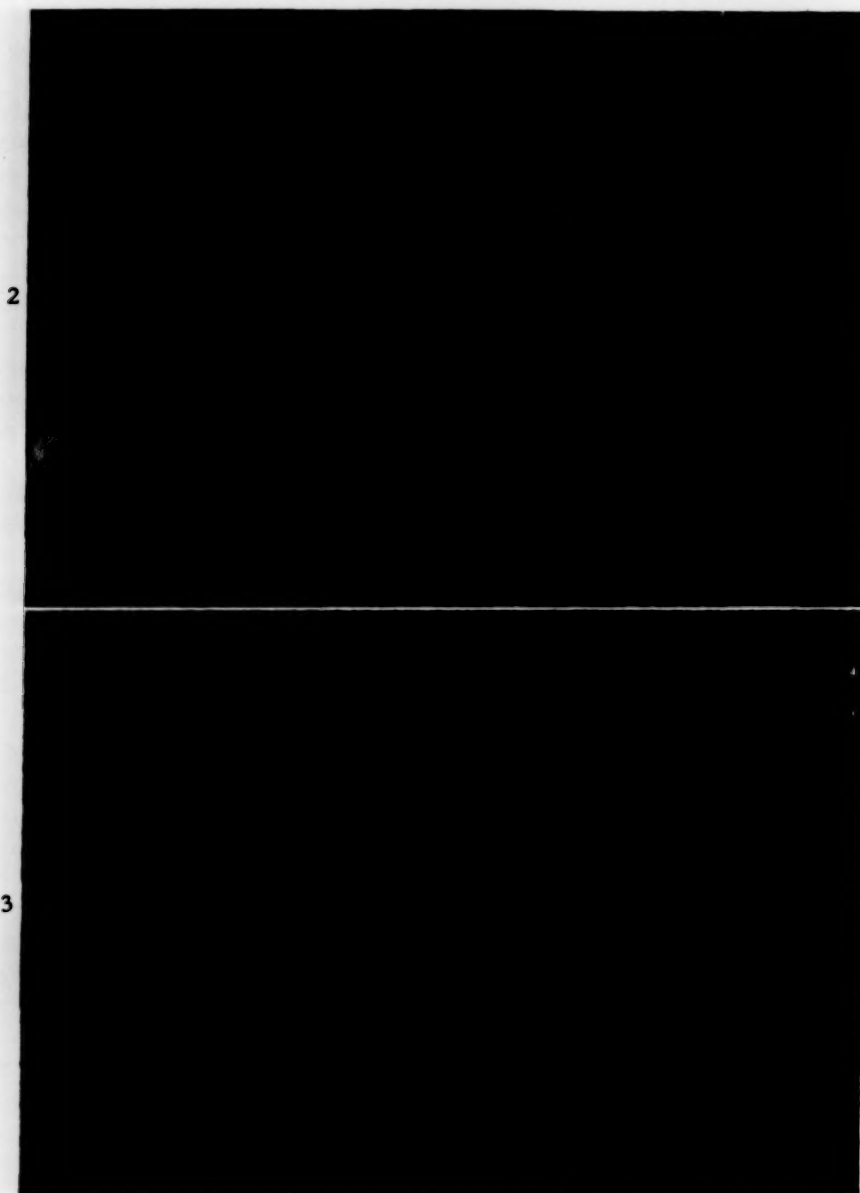


FIG. 2. Section of bone marrow from Case 1 (C. S.), demonstrating extensive infiltration by myeloma cells replacing almost all normal hemopoietic tissue.

FIG. 3. Section of kidney from Case 1 (C. S.) showing the classic changes of "myeloma" kidney. Of particular note is the cellular reaction to the protein material occluding the tubular lumen.

given empirically. Transfusions with packed red blood cells were ineffective in raising the hemoglobin. The patient's course was progressively downhill. On September 9th the pulse rose to 156/minute; there was tachypnea of 38/minute and hyperpyrexia of 104.6°F. (rectally). The patient became totally unresponsive and expired that day.

Autopsy was performed. On gross examination the bone marrow was pale and resembled that seen in aplastic anemia. The most remark-

able finding microscopically was almost complete replacement of the rib and vertebral marrow by myelomatous growth. (Fig. 2.) The kidneys were large and pale and both grossly and histologically demonstrated the typical findings of "myeloma kidney." (Fig. 3.) There was microscopic calcification in the mucosa of the stomach. (Fig. 4.) Extramedullary foci of hematopoiesis were present in the liver and spleen.

Comment. Although the total leukocyte count



FIG. 4. Section of stomach from Case 1 (C. S.) exhibiting calcification within the gastric mucosa.

was low normal (5,050/cu. mm.), there were only 30 per cent granulocytes. This was even more impressive when viewed in the light of the acute toxicity of the illness.

The correct etiologic diagnosis was not proved antemortem in this case although the working diagnosis (acute aplastic anemia) was apropos. Aspiration of the iliac crest or vertebral marrow might have clarified the etiology. Examination of the urine (4 plus albuminuria) for Bence-Jones protein might have been helpful. Lower nephron nephrosis due to myeloma has been described previously.¹⁰

CASE II. D. D., a sixty-nine year old retired janitor, arrived at the Emergency Room on May 24, 1952, because of severe epistaxis. Since he spoke almost no English the history was obtained from relatives.

For several months the patient had been having minor episodes of nosebleed usually associated with slight trauma. Four weeks prior to admission he had had his first major epistaxis followed by three more severe bouts, the most recent having been five days prior to admission. For the past six months the patient had malaise and anorexia and had lost 13 pounds.

Physical examination revealed a blood pressure of 122/60 mm. Hg. There was moderate pallor but no petechiae. The nasal septum was markedly deviated to the right and the right septal ridge was traumatized and actively bleeding; there was generalized oozing from the nasopharynx. The liver was palpable 4 cm. below

the right costal margin. There was no evidence of bleeding from the genitourinary or gastrointestinal tracts. The remaining physical findings were non-contributory.

Blood count on admission demonstrated a hemoglobin of 6.1 gm., red blood cell count of 1.82 million, white cell count of 3,650 with 74 per cent neutrophils (9 per cent juvenile forms), 2 per cent myelocytes, 2 per cent eosinophils, 1 per cent basophils, 15 per cent lymphocytes, 4 per cent monocytes and 1 per cent plasma cells. There was excessive rouleaux formation and the platelets were markedly diminished in the smear. Erythrocytic sedimentation rate was 16 mm./hr. (Wintrobe; corrected) and the hematocrit was 19 mm. Urine specific gravity was 1.022 and there was no sugar or albumin; the sediment was microscopically negative. The blood non-protein nitrogen was 62 mg. per cent and the fasting blood sugar 116 mg. per cent. Prothrombin time was 27 seconds (27 per cent of normal). Cephalin cholesterol, thymol turbidity, thymol flocculation and van den Bergh tests were all normal. Albumin-globulin ratio was 4.6:2.5 gm. per cent.

The epistaxis was arrested with great difficulty, requiring cauterization, oxycel® packing and repeated transfusions with whole blood. Three days after admission the patient developed progressively increasing tachycardia, tachypnea and hyperpyrexia. There was now a positive Babinski on the right, moderate nuchal rigidity and generally hyperactive deep tendon reflexes.

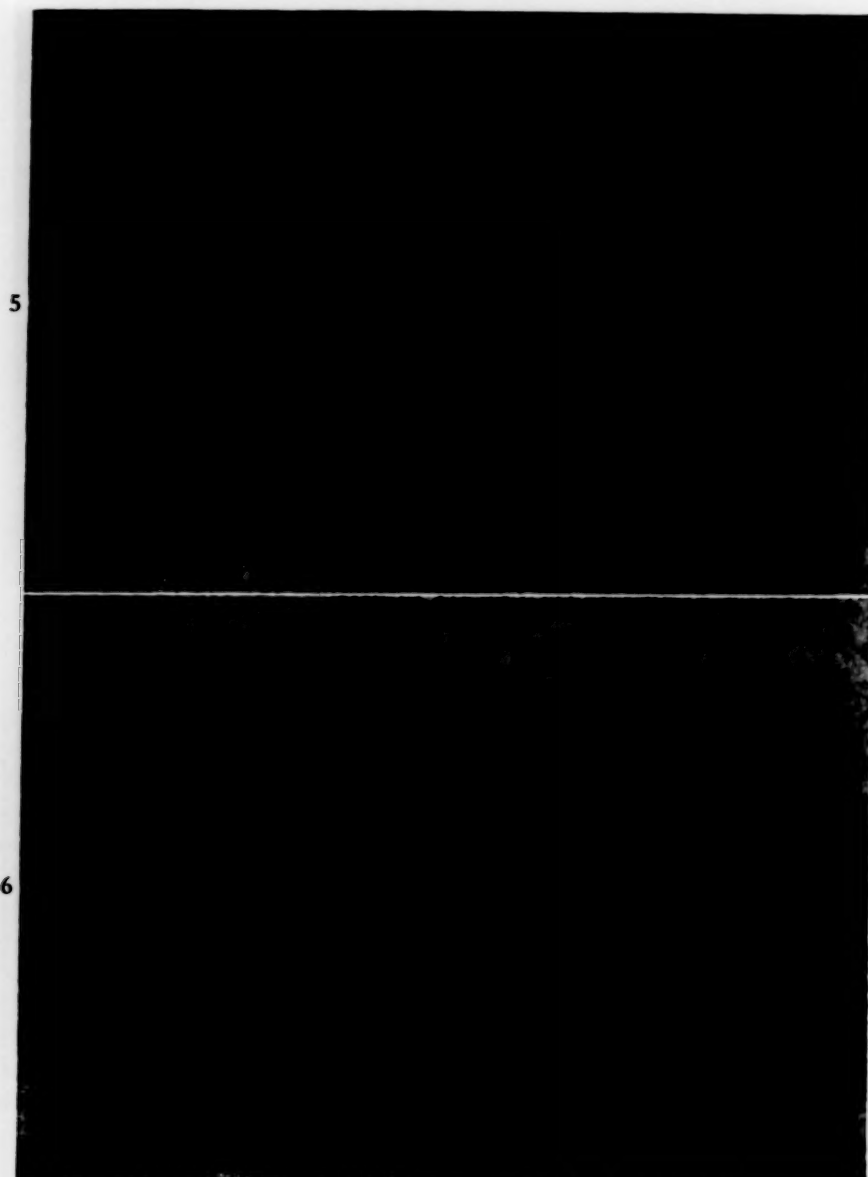


FIG. 5. Section of bone marrow from Case II (D. D.), with almost all normal hemopoietic tissue replaced by dense infiltration of myeloma cells.

FIG. 6. Section of kidney from Case II (D. D.) illustrating the usual findings of "myeloma" kidney.

The temperature the next day reached 105.8°F. (rectally). The patient became unresponsive and quietly expired.

Autopsy was performed and demonstrated the following pertinent findings. The liver was grossly normal. Microscopic examination of the liver and spleen revealed hematopoietic foci. Virtually all the functional marrow of representative sections of rib and vertebral column was replaced by a uniform cellular growth composed of plasma cells and their progenitors. (Fig. 5.) Subcapsular hemorrhages were present in both

kidneys and microscopically there were large numbers of dense hyalin casts distending and occluding segments of the distal convoluted tubules and collecting tubules. (Fig. 6.) In some instances there was desquamation in short ribbons attached to the casts, while in others there was a foreign body giant cell reaction to the occluding intratubular material. The lungs showed hypostatic pneumonia and patchy hemorrhagic extravasation. Permission to examine the brain could not be obtained.

Comment. Bleeding was the major problem in

this patient. The cause of hemorrhage in myeloma is a much discussed but poorly defined feature. The consensus has been that the usual factors involved in coagulation are normal^{2,5-7} and that abnormal proteins contribute to the deficiency in clotting. Although it has been repeatedly stated that the platelet count is usually normal, such is contrary to our experience in a series of fifty-eight myeloma cases.

Because of the rapid downhill course and preoccupation with control of recurrent epistaxis, investigative efforts were inadequate in this case. An antemortem marrow aspiration might have provided the diagnosis. The numerous ecchymoses and the apparent intracranial bleeding terminally suggested thrombocytopenia, and it is unfortunate that a platelet count was not made. The peripheral blood smear was almost devoid of platelets.

CASE III. E. C., a seventy-two year old housewife, had been followed elsewhere by hematologists. She was admitted to our hospital for the purpose of supportive care on January 8, 1953, with their diagnosis of aplastic anemia established by numerous recent examinations of marrow from the sternum and iliac crest. In addition to a long history of asthenia and lassitude the patient described some vague migratory pains. One week prior to admission she had sudden onset of pain in the "left side of my face" associated with swelling. This responded to a hip injection by her local physician.

Physical examination revealed mucosal petechiae and marked pallor. Blood pressure was 130/70 mm. Hg. The liver and spleen were both grossly enlarged and tender. The spleen extended almost to the iliac crest and the liver descended below the umbilicus. Other physical findings were non-contributory.

Blood count on admission revealed a hemoglobin of 6.6 gm., 2.02 million red blood cells and a white blood count of 3,850 with 52 per cent neutrophils and 26 per cent lymphocytes, 10 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. Platelet count was 16,000/cu. mm. Urinalysis exhibited a specific gravity of 1.007 with a faint trace of albumin and 4 to 6 hyaline casts per high power field. Blood non-protein nitrogen was 26 mg. per cent. Albumin-globulin ratio was 3.9:1.7 gm. per cent. One blood culture was obtained and remained sterile.

The patient received repeated blood transfusions and was discharged improved on January



FIG. 7. A typical myeloma cell from Case III (E. C.), representative of 20 per cent of the peripheral white blood cells and 91 per cent of the marrow cells.

22nd. Nine days later she developed pain, swelling and ecchymosis over the left temple. Concomitantly she became febrile and had severe pain of the abdomen, back and neck, requiring re-admission to the hospital February 6th.

Now there were widespread ecchymoses of the chest and abdomen and, in addition, the sternum and ribs were markedly tender. Because of the specific bone tenderness and our experience with two preceding cases, the diagnosis of multiple myeloma masquerading as aplastic anemia was entertained.

The hemogram on this admission was considerably improved due to the recent transfusions. Another blood culture again proved sterile. Three days later a blood smear revealed rouleaux formation, decreased platelets (only a rare giant form seen), and 20 per cent malignant reticular plasma cells or myeloma cells.

Bone marrow aspiration was performed the next day (February 10th). Although penetration of the sternum was abnormally easy, only with great difficulty could a small amount of greyish material be obtained. This contained more than the normal number of cells, 91 per cent of which were myeloma cells. (Fig. 7.)

On February 10th the patient gradually became unresponsive. The temperature, pulse and respiration continued rising as the blood pressure ebbed and the patient quietly expired that day. Permission for autopsy could not be obtained.

Comment. The numerous aplastic marrow samples obtained elsewhere suggest that the hypoplasia in aplastic anemia due to myeloma is

not attributable to replacement of normal hematopoietic tissue alone, since there were many islands of aplastic marrow with no myeloma tissue. The temporal lesion was undoubtedly a myeloma nodule but unfortunately skull x-rays were not made.

OBSERVATIONS

The fact that in a series of fifty-eight cases of multiple myeloma three presented as aplastic anemia raises the question of whether myeloma has been missed in other cases of aplastic anemia. It seems likely that if myeloma is sought more diligently in cases of pancytopenia, this combination will prove to be more common than is presently supposed.

A single non-productive bone marrow aspiration or even repeated negative aspirations from the same bone are not sufficient to exclude the diagnosis of myeloma. As stated by Begemann,⁹ one must perform repeated aspirations from various bones in order to clarify the diagnosis in cases of marrow aplasia. We would like to emphasize that there is rarely, if ever, a "dry tap" in bone marrow aspiration. If one is certain he is in the marrow cavity, there is almost always diagnosable material within the needle lumen. This material may have the appearance of serum and give no gross indication of containing blood. It should nevertheless be smeared and stained for examination. Care must be taken also not to aspirate a previously irradiated bone. Similar confusion may devolve following use of radioactive phosphorus or other marrow toxic agents.

When the results of marrow aspiration are repeatedly of no aid in diagnosis, surgical biopsy is indicated. This affords a certain means of obtaining marrow tissue.

The presence of marked hypoplasia in marrow not replaced by myeloma tumor supports the thesis that hematopoiesis suffers some sort of metabolic (toxic) inhibition in multiple myeloma. Diffusely infiltrating myeloma probably

enhances unusually severe anemia in two ways: (1) extensive replacement of normal marrow and (2) toxic inhibition of hematopoiesis by secretions from an unusually large total mass of myeloma tissue.

SUMMARY AND CONCLUSIONS

1. Three cases of multiple myeloma which simulated aplastic anemia antemortem are presented.

2. The incidence (5.2 per cent) of this combination in a series of fifty-eight histologically proven cases of multiple myeloma suggests that myeloma must be included in the etiology of aplastic anemia.

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Review

Hemophilia and Hemophilia-like Diseases Caused by Deficiencies in Plasma Thromboplastin Factors:*

Anti-hemophilic Globulin (AHG), Plasma Thromboplastin Component (PTC) and Plasma Thromboplastin Antecedent (PTA)

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HEMOPHILIA usually has been considered a hereditary hemorrhagic disease related to a specific defect in a single clotting factor, anti-hemophilic globulin. It is characterized by occurrence in males and transmission as a sex-linked recessive trait by female carriers; by prolonged clotting time and impaired prothrombin utilization; and by normal values for platelet count, clot retraction, prothrombin time, tourniquet test and bleeding time. Recent studies have revealed, however, that any one of three different defects in the blood clotting mechanism will cause the clotting characteristics and clinical picture of hemophilia. The occurrence of more than one type of clotting deficiency as a cause of hemophilia-like disease has been suggested by mutual correction of the clotting defect in a mixture of bloods obtained from two subjects presenting the usual findings of hemophilia. Observations of this sort have been recorded by Pavlovsky,¹ Koller et al.,² Aggeler et al.,³ Schulman and Smith,⁴ Poole,⁵ Biggs et al.⁶ and Rosenthal et al.⁷ Further identification of the clotting factors indicates that the cases reported by Biggs et al.⁶ are identical with the case of plasma thromboplastin component (PTC) deficiency reported by Aggeler et al.³ Further studies by Rosenthal et al.⁷ have established a third plasma thromboplastin defect called plasma thromboplastin antecedent (PTA) deficiency. They showed that the type of plasma

thromboplastin defect could be evaluated on the basis of the corrective effects of normal serum and BaSO₄-treated plasma as follows:

	Corrected by:	
	Serum	BaSO ₄ -treated Plasma
Anti-hemophilic globulin (AHG) deficiency.....	No	Yes
Plasma thromboplastin antecedent (PTA) deficiency.....	Yes	Yes
Plasma thromboplastin component (PTC) deficiency.....	Yes	No

In addition, variable degrees in the severity of the clotting defect in true hemophilia have been recognized. Thus the clotting time may be normal or only slightly elevated as reported by Merskey,⁸ Quick and Hussey⁹ and Graham, McLendon and Brinkhous.¹⁰

This paper presents a study of thirty-three patients with overt hemophilia or hemophilia-like disease and eleven carriers. Its purpose is to elucidate the clinical and coagulation characteristics of each type of deficiency.

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METHODS

Histories were taken and physical examinations were performed, with particular emphasis placed upon the pattern and severity of hemorrhage, joint involvement and postoperative bleeding. Family histories were studied for

centrifuged plasma. Matching or mixing studies were performed in each case in order to identify the type of coagulation defect. All coagulation tests were performed at 37°C.

Modified Lee-White clotting time and heparin clotting time procedures were carried out ac-

TABLE I
CONTROL VALUES OF CLOTTING TESTS AND THEIR INTERPRETATION

Test	No. of Control Subjects	Mean Value (min.)	S.D. *	Mean \pm 2 S.D. (min.)	Range (min.)	Remarks
Clotting time	98	8.2	1.5	5.2-11.2	4-12	Prolonged if more than 12 min.
Heparin clotting time (4 gamma)	99 *	26.4	4.0	18.4-34.4	17-37	Prolonged if more than 35 min.
	33†	27.5	3.6	20.3-34.7	20-35	
Recalcified plasma clotting time	Slowly centrifuged (platelet-rich)			Normal less than 2½ min.		
	Rapidly centrifuged (platelet-poor)			Normal less than 4½ min.		
Serum prothrombin time	Less than 20 sec. — Abnormal utilization of prothrombin					
	21 to 25 sec. — Borderline, possibly abnormal					
	More than 26 sec. — Normal utilization of prothrombin					
Prothrombin time	12 to 17 sec.		— Normal, depending upon the daily control value for the thromboplastin.			

* Series of subjects studied in New York, 1950 to 1951.

† Series of subjects studied in Berkeley, Calif., 1947 to 1948.

indications of abnormal bleeding. The coagulation studies were performed in an interim period in which there was no active hemorrhage. No treatment had been given for at least four days prior to study of patients with AHG deficiency and at least two months prior to study of patients with PTC and PTA deficiencies.

Blood for the coagulation studies was drawn with a dry glass syringe and a 19- or 20-gauge needle. Particular care was taken to enter the vein cleanly in order to minimize admixture of the blood with tissue juice and air. If the venepuncture was unsatisfactory, the sample was not used for study. The first and last cc. of blood in the syringe were discarded as recommended by Jaques.¹¹

The following studies were performed: platelet count, clotting time, heparin clotting time, observation of clot retraction, prothrombin time, bleeding time, tourniquet test and recalcified plasma clotting time of slowly and rapidly

cording to methods described in a previous report.¹² The end point of clotting was timed from the appearance of the blood in the syringe to the formation of a firm clot upon inversion of the test tube. To determine the clotting time 1 cc. of blood was placed in a glass tube 13 mm. by 100 mm. in size. A similar procedure was used for the heparin clotting time in which the 1 cc. of blood, measured from the syringe, was added to and mixed with 4 gamma or micrograms of heparin dissolved in 0.1 cc. of 0.85 per cent saline. The prothrombin time was performed by the one-stage Quick method, using rabbit brain thromboplastin.¹³ The serum prothrombin time was estimated by a modification of the one-stage methods described by Quick¹⁴ and by Dreskin.¹⁵ In the test, serum was removed from the tube used for the measurement of the clotting time one to one and one-half hours after clotting. If clot retraction was adequate, 0.1 cc. of serum was taken directly

TABLE II
CLINICAL AND CLOTTING DATA IN PATIENTS WITH ANTI-HEMOPHILIC GLOBULIN (AHG), PLASMA THROMBOPLASTIN COMPONENT (PTC) AND PLASMA THROMBOPLASTIN ANTECEDENT (PTA) DEFICIENCIES

Case No.	Sex	Age (yr.)	Family History	Pattern of Hemorrhage					Present Activity	Date of Study (mo./yr.)	Clotting Time (min.)	Heparin Clotting Time (min.)	Serum Prothrombin Time (sec.)	Prothrombin Time (sec.)	Plasma Clotting Time		Date of Previous Test (mo./yr.)	Clotting Time Result (min.)
				Circumcision	Joints	Skin	Tooth Extrac-tion	Hema-turia							Epistaxis	Post-operative		
Anti-hemophilic Globulin (AHG) Deficiency																		
1	M	15	Neg.	+++	++	++	+++	++	++	3/53	10	38	16	14	3	5-6	4/49	8
2	M	15	Neg.	+++	++	++	+++	++	++	4/53	15	240	15	14	6½-7½	18-28	4/49	8
3	M	5½	Pos.	+++	++	++	+++	++	++	6/53	15	96	8	15	6¾-7	14-17	7/51	17
4	M	19	Neg.	+++	++	++	+++	++	++	6/53	15	85	11	14	4-4½	11-15	7/51	17
5	M	2	Neg.	+++	++	++	+++	++	++	3/53	18	132	7	14	6¾-7¾	10-13	8/47	13
6	M	28	Neg.	+++	++	++	+++	++	++	1/53	18	150	7	15	4¾	13	8/47	13
7	M	41	Pos.	+++	++	++	+++	++	++	3/53	18	>240	9	14	4-4½	10-11½	11/48	20
8	M	22	Neg.	+++	++	++	+++	++	++	4/53	22	50	5	14	5½	10-11½	11/48	15
9	M	5	Neg.	+++	++	++	+++	++	++	1/53	24	161	15	16	5	14-28	11/48	44
10	M	24	Pos.	+++	++	++	+++	++	++	4/53	31	>240	7	14	46	44
11	M	20	Neg.	+++	++	++	+++	++	++	4/53	40	>240	10	14	39	180
12	M	3	Neg.	+++	++	++	+++	++	++	12/52	42	180	10	14	11	12-30	8/47	60
13	M	8	Neg.	+++	++	++	+++	++	++	1/53	45	>240	14	14	8½	17	8/47	75
14	M	6	Pos.	+++	++	++	+++	++	++	8/52	47	>240	12	12	6/49	65
15	M	55	Neg.	+++	++	++	+++	++	++	12/52	46	>240	13	13	11	12-36	6/49	75
16	M	17	Pos.	+++	++	++	+++	++	++	3/53	58	>240	7	15	8-10	12-22	6/49	65
17	M	16	Pos.	+++	++	++	+++	++	++	3/53	70	>240	6	14	5-7	11-16	7/46	66
18	M	16	Pos.	+++	++	++	+++	++	++	3/53	70	>240	7	15	7-12	12-30	9/52	66
19	M	18	Pos.	+++	++	++	+++	++	++	4/53	65	>240	9	12	7-8	17-40	9/52	66
20	M	12	Pos.	+++	++	++	+++	++	++	5/53	75	>240	15	14
21	M	16	Pos.	+++	++	++	+++	++	++	6/53	48	>240	11	12
Plasma Thromboplastin Component (PTC) Deficiency																		
22	M	53	Pos.	+++	++	++	+++	++	++	3/53	8	39	12	12	4	5	1/53	6
23	M	19	Pos.	+++	++	++	+++	++	++	3/53	7	53	13	15	2½	5½	5/52	7
24	M	6	Pos.	+++	++	++	+++	++	++	7/52	12	31	16	14	6	13	1/49	11
25	M	42	Pos.	+++	++	++	+++	++	++	2/53	15	65	10	14	6	8½	8/52	36
26	M	4	Neg.	+++	++	++	+++	++	++	1/53	35	>240	11	14	8-9	17-25	8/52	36
27	M	5	Pos.	+++	++	++	+++	++	++	4/53	40	12	13	5	10-11
Plasma Thromboplastin Antecedent (PTA) Deficiency																		
28	M	45	Pos.	+++	++	++	+++	++	++	3/53	7	39	18	15	2½	4½-5	9/52	8
29	M	22	Neg.	+++	++	++	+++	++	++	3/53	8	39	16	16	3½	5	9/52	8
30	M	43	Neg.	+++	++	++	+++	++	++	2/53	9	40	17	15	3½	6	3/53	13
31	F	29	Pos.	+++	++	++	+++	++	++	5/53	24	>240	11	15	7-8	7-8	3/53	13
32	F	25	Pos.	+++	++	++	+++	++	++	4/53	29	>240	8	15	4	10-17	5/50	17
33	M	51	Pos.	+++	++	++	+++	++	++	8/52	20	>240	17	17	5	10-15	5/50	15

*T & A = tonsillectomy and adenoidectomy.

†I & D = incision and drainage.

‡Ap = appendectomy.

Relations: No. 16 maternal uncle of No. 17.

No. 23 and No. 24 are cousins.

No. 21 maternal uncle of No. 22.

No. 27 and 32 brothers and maternal uncles of sisters Nos. 30 and 31.

Degree of hemorrhage: + slight; ++ moderate; +++ marked.

from the clotting tube by a calibrated capillary pipette without disturbing the clot. If necessary, the tube was centrifuged for about three minutes in order to free the serum from the clot for removal. The test was then performed within five minutes after the removal of the serum from

and interpretation of the various clotting tests are listed in Table I.

Mixture or matching experiments¹⁶⁻¹⁹ were performed on various combinations of whole blood and oxalated plasma from patients, normal subjects and carriers, as will be described.

TABLE III
MATCHING STUDIES PERFORMED ON AHG-DEFICIENT BLOOD

0.1 cc.	Plus	1 cc. Blood					
		Case 18 AHG Deficiency			Case 7 AHG Deficiency		
		Clotting Time (min.)	Serum Prothrombin Time (sec.)	Correc- tion *	Clotting Time (min.)	Serum Prothrombin Time (sec.)	Correc- tion
Nothing added.....	70	6	18	9	
Normal serum.....	12	6	0	12	7	0	
Normal BaSO ₄ -treated plasma.....	8	24	+++	10	24	+++	
Plasma, AHG-deficient, Case 16, frozen 14 days, thawed and refrozen twice.....	25	8	0	15	12	0	
Plasma, PTC-deficient, Case 24, frozen 16 days, thawed and refrozen twice.....	10	18	++	10	19	++	
Plasma, PTA-deficient, Case 31, frozen 11 days, thawed and refrozen twice.....	10	18	++	10	16	++	
As above, Case 31, plasma never thawed previously.....	10	22	++	

* Degree of correction: 0 none; + slight; ++ moderate or partial; +++ marked or almost complete.

the clot on a mixture of 0.1 cc. test serum, 0.1 cc. BaSO₄-adsorbed normal plasma, 0.1 cc. rabbit brain thromboplastin emulsion and 0.1 cc. 0.025 M CaCl₂.

Test samples for the recalcified plasma clotting time were prepared as follows: 4.5 cc. of blood was mixed with 0.5 cc. of 0.1 N sodium oxalate in a conical glass centrifuge tube. As soon as possible after collection of the blood, the tube was centrifuged at 500 r.p.m. (about 180 g.) for ten minutes and a sample of platelet-rich, slow-centrifuged plasma was removed. The tube was then returned to the centrifuge and centrifuged for thirty minutes at 1,500 r.p.m. (about 580 g.). The plasma removed was the platelet-poor, rapidly centrifuged sample. In testing, 0.2 cc. of 0.025 M CaCl₂ was added to 0.2 cc. of plasma and the clotting time was measured. In instances in which the plasma clotting times were greatly prolonged, the times of the initial appearance of fibrin and formation of a firm clot were both recorded. Control values

Detailed descriptions and evaluations of these techniques will be reported elsewhere. Samples of frozen plasma used in these experiments were stored at -20°C. The presence of a circulating anticoagulant was studied by the methods of Conley et al.²⁰ and Dreskin and Rosenthal.²¹

RESULTS

Diagnosis. The history of abnormal bleeding phenomena raised the question of a clotting defect in each of the patients, as shown in Table II. A prolonged clotting time and heparin clotting time, impaired utilization of prothrombin, as reflected by the serum prothrombin time, and prolongation of the recalcified plasma clotting time, together with normal prothrombin time, platelet count, clot retraction, tourniquet test and bleeding time, all consistent with the diagnosis of hemophilia, were noted in a majority of the patients. In this series of cases the seven patients with clotting times in the normal range (Table II, patients #1, 22, 23, 24, 28, 29 and 30)

all exhibited prolonged heparin clotting time, impaired utilization of prothrombin and prolonged recalcified plasma clotting time.

Identification of the clotting defects present in these patients was accomplished by matching experiments in which the corrective effect of

defect. Tables III, IV and V present typical results obtained in blood samples deficient in AHG, PTC and PTA. In these tests 1 cc. aliquots of freshly drawn test blood were mixed in a series of tubes with 0.1 cc. of normal serum, BaSO₄-treated normal plasma and plasma sam-

TABLE IV
MATCHING STUDIES PERFORMED ON PTC-DEFICIENT BLOOD

0.1 cc.	Plus 1 cc. Blood					
	Case 24 PTC Deficiency			Case 7 PTC Deficiency		
	Clotting Time (min.)	Serum Prothrombin Time (sec.)	Correc- tion *	Clotting Time (min.)	Serum Prothrombin Time (sec.)	Correc- tion
Nothing added	6	11	7	13
Normal serum	5	50	+++
Normal BaSO ₄ -treated plasma	5	13	0
Plasma, PTC-deficient, Case 25, frozen 33 days	5	11	0
Plasma, AHG-deficient, Case 17, fresh	7	22	++
Plasma, PTA-deficient, Case 32, frozen 34 days	11	23	++
Plasma, PTC-deficient, Case 24, frozen 1 day	7	14	0

* Degree of correction: see footnote of Table III.

TABLE V
MATCHING STUDIES PERFORMED ON PTA-DEFICIENT BLOOD

0.1 cc.	Plus 1 cc. Blood					
	Case 31 PTA Deficiency			Case 32 PTA Deficiency		
	Clotting Time (min.)	Serum Prothrombin Time (sec.)	Correc- tion *	Clotting Time (min.)	Serum Prothrombin Time (sec.)	Correc- tion
Nothing added	13	11	29	8
Normal serum	4	44	+++
Normal BaSO ₄ -treated plasma	8	44	+++
Plasma, AHG-deficient, Case 16, frozen 38 days	8	34	+++
Plasma, PTC-deficient, Case 24, frozen 40 days	6	30	+++
Plasma, PTA-deficient, Case 31, frozen 35 days	13	14	0

* Degree of correction: see footnote of Table III.

normal serum and normal BaSO₄-treated plasma was evaluated. In addition, various combinations of patients' plasma were mixed, in order to check further the identity of the

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ples obtained from patients with previously identified plasma thromboplastin defects. The degree of correction was evaluated by the extent of return of prothrombin utilization to-

ward normal. (Table I.) The lowering of the clotting time to normal was a less specific index of correction.

Results of studies performed on two patients identified as having AHG deficiency are shown in Table III. There was no correction of the clotting defect by normal serum or by a previously identified AHG-deficient plasma. However, plasma from subjects deficient in PTC and PTA corrected the defect to a moderate extent. Failure to achieve more complete correction, as judged by the restoration of the serum prothrombin time and hence prothrombin utilization toward normal, is attributed to the disappearance of AHG during storage, thawing and refreezing of the frozen samples. PTA-deficient plasma which was kept frozen for eleven days without thawing restored the serum prothrombin time to twenty-two seconds as compared with eighteen seconds obtained with identical plasma which had been thawed and refrozen twice.

In PTC-deficient patients (Table IV) normal serum produced excellent correction of the clotting defect while BaSO₄-treated plasma and PTC-deficient plasma had no effect. The corrective effects of AHG- and PTA-deficient plasmas are also shown.

In PTA deficiency both normal serum and BaSO₄-treated plasma corrected the clotting defect. (Table V.) The defect was also corrected by AHG- and PTC-deficient plasmas but was not corrected by PTA-deficient plasma.

These mixture studies have been further corroborated in many instances by evaluation of the corrective effects of mixtures of whole blood drawn simultaneously from two or more subjects.^{7,22} Determination of the recalcified plasma clotting times of mixtures of oxalated plasma obtained from different subjects has also provided further checks on the results.

Incidence of AHG, PTC and PTA Deficiencies. As shown in Table VI, AHG deficiency was identified in twenty or 74 per cent of the twenty-seven families. PTC deficiency was found in 15 per cent and PTA deficiency in 11 per cent of the families. The relation between the clotting time and type of deficiency is of interest. (Table VII.) In the group of twenty-one patients with AHG deficiency the clotting times ranged from ten to seventy-five minutes, and seven patients had clotting times above fifty minutes. The PTC patients had clotting times ranging from normal values to forty minutes, with three patients in the five- to twelve-minute normal range. The

clotting times of the PTA-deficient patients were all below thirty minutes, with three subjects in the normal range. Although this series is small, these findings suggest that the majority of patients with clotting times above thirty minutes, and particularly those above fifty

TABLE VI
INCIDENCE OF SEX, HEREDITARY HISTORY AND CARRIERS IN
AHG, PTC AND PTA DEFICIENCIES

	No. of Cases		
	AHG Deficiency	PTC Deficiency	PTA Deficiency
Males	21	6	4
Females	0	0	2
Families, number	20	4	3
Family history positive	10	5	4
Family history negative	11	1	2
Carriers studied	7	3	1
History of abnormal bleeding	1*	1	0
Possible clotting defect	2	2	1

* Does not include the mother of Case 1 (AHG deficiency), who gives a history of easy bruising.

TABLE VII
CLOTTING TIME IN AHG, PTC AND PTA DEFICIENCIES

Clotting Time (min.)	No. of Cases			Total
	AHG Deficiency	PTC Deficiency	PTA Deficiency	
5 to 12 (normal range)	1	3	3	7
13 to 30	8	1	3	12
31 to 50	5	2	..	7
Over 50	7	7
Total	21	6	6	33

minutes, have AHG deficiencies. On the other hand, a majority of these patients with clotting times in the normal range appear to have PTC or PTA deficiencies.

Pattern of Hemorrhage. The hemorrhagic manifestations for each patient in the series are listed in Table II. Although the clinical manifestations of hemorrhage are subject to many factors dependent not only upon the presence of a

clotting defect but upon the precautions taken to minimize hemorrhage by avoidance of trauma, surgical procedures and physical activity, certain conclusions can be drawn. The patients with AHG deficiency were more frequently subject to bleeding into the joints and

deficiency indicates a pattern of transmission similar to that of AHG deficiency. The lineage of a PTC-deficient family is presented in Figure 1. It is apparent that the disease is transmitted by female carriers to males, and that affected males can transmit the gene as a recessive trait

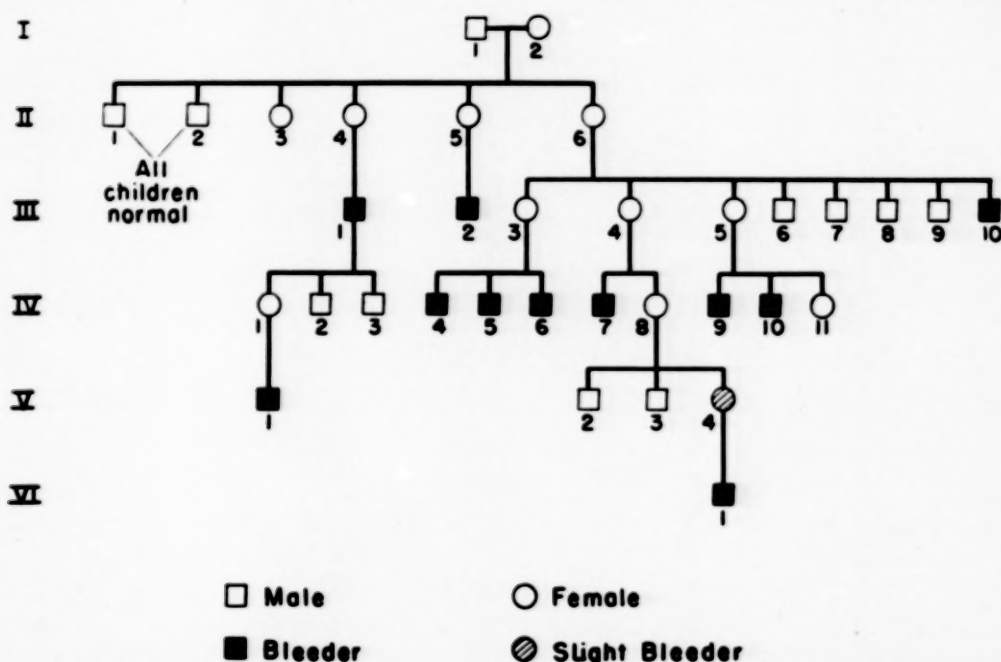


FIG. 1. Genealogy of a family with plasma thromboplastin component (PTC) deficiency; iv 6 is Case 23; vi 1, Case 24 in the present study; iii 3 is carrier 42 and v 4 carrier 41.

skin and to hematuria. These bleeding manifestations appear to be rare in the PTA-deficient patients, in whom bleeding particularly follows tooth extraction and certain minor surgical procedures, but rarely involves the joints. In PTC deficiency the bleeding seems to be more severe than in PTA deficiency but somewhat less severe than in patients with AHG deficiency.

There is some relation between the degree of clotting time prolongation and the severity of hemorrhage. As the patients with clotting times above thirty minutes reach adult life there is more chance of incapacitation, usually due to unresolved hemarthrosis (Cases 10, 15, 16, 18 and 19), than in patients with clotting times below thirty minutes.

Sex and Hereditary Aspects (Table vi). All patients with AHG and PTC deficiencies were males. In the PTA-deficient group two of the patients were females, the remainder males. The findings in the AHG-deficient group are uniformly consistent with a sex-linked recessive trait carried by the female and transmitted to the male. Study of our two families with PTC

to females. Studies on transmission of PTA deficiency are in progress and will be reported later. The trait is not sex-linked, possibly dominant and can be transmitted either to males or females.

Case No. 27 (PTC deficiency) was the only Negro in the group.

Carriers. Eleven carriers* were studied, as shown in Tables vi and viii. One (No. 34) gave a history of easy bruising and unusual bleeding after a tonsillectomy; another (No. 41) gave a history of marked bleeding following a tooth extraction. The mother of Case No. 1 gave a history of easy bleeding but no clotting studies were performed. The low serum prothrombin times suggested minimal clotting defects in subjects Nos. 34 and 35 (AHG carriers) and

* The term "carrier" is used to designate a person who transmits the disease without himself having any overt manifestation of the disease. It is possible that the carrier, as so defined, may or may not exhibit mild symptoms and laboratory evidences of the trait. In accordance with this interpretation of the term "carrier," subject No. 44 has been designated a PTA carrier, pending further clarification of the transmission of PTA deficiency.

No. 43 (PTC carrier). Subject No. 42 (PTC carrier) had a more definite clotting defect as judged by the heparin clotting time of thirty-five minutes and serum prothrombin time of thirteen seconds. Plasma from this subject did not correct the clotting defect of her son's

and PTA deficiencies in clotting pattern at comparable degrees of prolongation in the clotting time. An anticoagulant was present only in Case 19.

The consistency of the clotting times obtained during quiescent periods in patients studied at

TABLE VIII
BLOOD COAGULATION STUDIES PERFORMED IN ELEVEN FEMALE CARRIERS

Subj. No.	Patient No. and Relation	Clotting Defect	Abnormal Bleeding History	Clotting Time (min.)	Heparin Clotting Time (min.)	Serum Prothrombin Time (sec.)	Prothrombin Time (sec.)	Recalcified Plasma Clotting Time (min.)	
								Slowly Centrifuged Plasma	Rapidly Centrifuged Plasma
35	2, Mother	AHG	Pos.	7.5	28	22	15	2.25	4
35	2, M.G.M.*	AHG	Neg.	8	28	18	15	2.5	4.25
36	5, Mother	AHG	Neg.	9	22	38	14	2	3
37	9, Mother	AHG	Neg.	5	20	45	14
38	10, Mother	AHG	Neg.	7	29	39	14	1.75	2
39	16, Mother	AHG	Neg.	7	28	26	15	2	4
40	17, Mother	AHG	Neg.	8	25	31	14	2	3.5
41	23, Mother	PTC	Pos.	5	21	29	14	2.5	3.5
42	24, Mother	PTC	Neg.	10	35	13	16	3	4.5
43	25, Mother	PTC	Neg.	5	..	23	13
44	30,31, Mother	PTA	Neg.	10	28	18	14	5	7.25

* Maternal grandmother.

plasma as well as did normal plasma. It is interesting to note, however, that her blood, transfused to her son, was effective in checking hemorrhage. Subject No. 44 (PTA carrier and sister of patient No. 33) had a definite clotting defect as revealed by abnormal utilization of prothrombin, and her fresh plasma did not correct the clotting defect of her daughter (patient No. 32).

Coagulation Studies. These studies are presented in Table II. Control values and interpretation of the clotting tests are shown in Table I. Relationships among the clotting time and heparin clotting time, serum prothrombin time and plasma clotting time are shown in Figure 2. The patients with prolongation in clotting time invariably revealed abnormal values for the heparin clotting time, serum prothrombin and recalcified plasma clotting times of both slowly and rapidly centrifuged plasma. The patients with normal clotting times revealed slight but usually definite abnormal values in the other tests (Cases 1, 22, 23, 24, 28, 29 and 30). There were no apparent differences among AHG, PTC

intervals several years apart is revealed in Cases 1, 4, 6, 7, 9, 10, 13, 14, 15, 18, 19, 24, 32 and 33.

COMMENTS

In this study of a series of patients with hemorrhagic disease an attempt was made to elucidate the clinical and blood coagulation characteristics resulting from deficiencies in plasma thromboplastin factors. Deficiency in any one of three plasma clotting factors which react with platelets to form thromboplastin can give the clinical and blood clotting abnormalities previously considered diagnostic of hemophilia. These cases can be distinguished by matching studies and evaluation of the corrective effects of normal serum and normal BaSO₄-treated plasma on the clotting defect, as indicated in Table IX.

Certain features of AHG, PTC and PTA deficiencies are recorded in Table IX. AHG and PTC deficiencies appear to be inherited in a similar manner, as sex-linked recessive traits transmitted by the female carrier to the male. Biggs et al.³ have found a similar hereditary

pattern in PTC deficiency. Studies are in progress on the transmission of PTA deficiency. It can be stated that it is not sex-linked, and can be transmitted probably by female and male carriers to children of either sex.

Minor expressions of the clotting deficiency

hemophilia. Carriers of severe AHG and PTC deficiency were completely normal in our study. In PTA deficiency the only carrier studied revealed a slight but definite clotting defect.

Although the occurrence of hemorrhage is dependent upon numerous factors in addition to

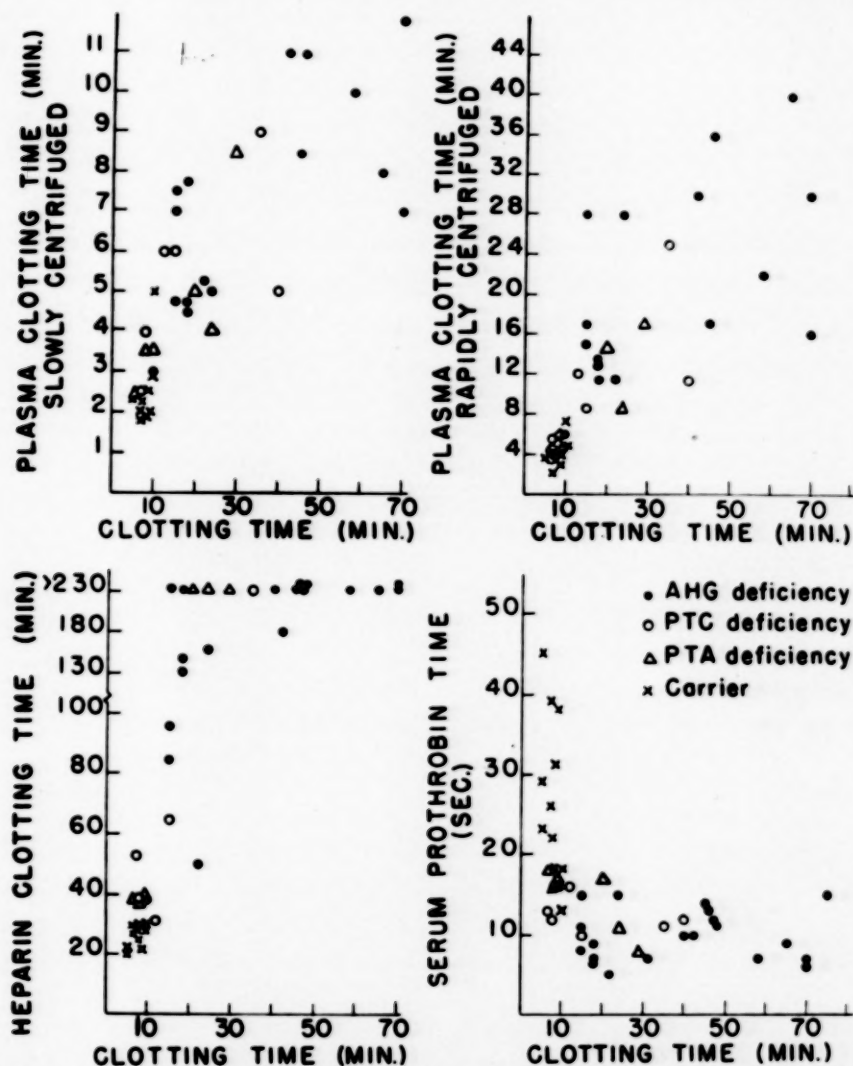


FIG. 2. Relation between clotting time and heparin clotting time, serum prothrombin time and the recalcified plasma clotting time of slowly and rapidly centrifuged samples in patients with AHG, PTC and PTA deficiencies and in carriers.

and hemorrhagic tendency may appear in the carrier state, as reviewed by Merskey and Macfarlane.²³ Our studies indicate that in the mild forms of both AHG and PTC deficiency carriers seem to have slight clotting defects associated with normal clotting times. Graham et al.¹⁰ found slight abnormalities in prothrombin utilization and diminished AHG levels in the blood of female carriers in a family with mild

defects in blood clotting, certain differences among AHG, PTC and PTA deficiencies are apparent.

Hemorrhage is most severe in AHG deficiency, followed in severity by PTC and then by PTA deficiency. Involvement of joints is frequent in AHG deficiency, occasional in PTC deficiency and rare in PTA deficiency. PTA deficiency is most prominently characterized by bleeding

after tooth extraction or other minor surgical procedures.

The relation between the bleeding tendency and the severity of the clotting defect is of interest. In each type of plasma thromboplastin deficiency the severity of hemorrhage and disability bears a direct relation to the degree of clotting defect. Under certain conditions of stress, however, as during surgery or following trauma, patients with slight defects are subject to severe and sometimes fatal hemorrhage. This situation, also discussed by Graham et al.,¹⁰ possibly arises from the initial blood loss, resulting in depletion of the supply of already deficient clotting factor. As the patient does not have the reserve with which to replace the deficient factor, a slight defect can readily become severe. It is also possible that under certain adverse conditions formation of the already deficient clotting factor may become further impaired.

The severity of the clotting defect and hemorrhage appears to be reflected in the degree of prolongation of the clotting time, as has been found by Merskey.¹⁷ In AHG deficiency Graham et al.¹⁰ found that in severe cases with prolonged clotting times the concentration of AHG is less than 5 per cent of normal, and in cases with normal or only slightly prolonged clotting time the concentration is below 19 per cent. If the clotting time is to be depended upon, however, it is important to emphasize the need to standardize its performance. We have found that the method used in this study provides consistent and easily standardized results. The use of smaller tubes, multiple tubes, variations in the amount of blood in the tube and in room temperature provide uncontrolled variables in the method and make interpretation of the results very difficult. In cases with prolonged clotting time the deficiency is sufficiently severe to give markedly abnormal values in the heparin clotting time or heparin tolerance,²⁴ recalcified plasma clotting time of slowly and rapidly centrifuged plasma,^{17,25} and serum prothrombin time or rate of prothrombin utilization.^{14,26} The clotting time, however, is a relatively insensitive test of the clotting mechanism and a normal value does not rule out the possibility of a clotting defect.^{12,27} In these cases the heparin clotting time and serum prothrombin time are more sensitive tests. The presence of a very slight defect, however, frequently has been very difficult to detect, even by these latter tests. Evalua-

tion of the effects of serum, BaSO₄-treated plasma and plasmas deficient in various factors on prothrombin utilization of the subjects' blood is necessary to clarify the diagnosis. Assay of the deficient clotting factor by the methods of Brinkhous' group^{16,28} and of Soulier²⁴ should be of value in these mild cases.

In patients with hemophilia-like disease and clotting time prolonged above thirty minutes, AHG deficiency is most frequently encountered, while PTC deficiency is rarer, as has been found by Biggs et al.⁶ and Soulier and Larrieu.²⁴ In patients with normal or only slightly prolonged clotting times, however, PTC and PTA deficiencies may be more prevalent than AHG deficiency. In the series of seven PTC-deficient cases reported by Biggs et al.⁶ five had clotting times of less than sixteen minutes.

On the basis of studies now in progress it appears that many patients with a history of abnormal bleeding, particularly after tooth extraction, with normal clotting time and heparin clotting time, have either PTC or PTA deficiencies. During interim periods, however, these patients may reveal normal coagulability and it is difficult to establish the diagnosis with certainty. It is necessary to study these patients several times, particularly during active bleeding or stress periods, before the clotting defect can be definitely evaluated. Many patients who have been classified previously as thrombasthenia or as having abnormal vascular fragility may actually have slight PTA or PTC deficiencies.

It is not within the scope of this paper to discuss treatment in detail other than to mention a few generalities. Treatment should be directed toward control of bleeding by direct or local measures, reduction of any existing stress and effective replacement of the deficient clotting factor by the administration of appropriate substances. The plasma thromboplastin factors present in various fractions of plasma are shown in Table ix. As AHG disappears during storage in a refrigerator it is imperative either to replace it by administration of fresh blood, if anemia has developed, or by fresh or fresh-frozen plasma. Serum does not contain AHG, which is consumed during the clotting process. On the other hand, PTC^{3,6,29} and PTA⁷ are not consumed during clotting but appear to be potentiated by the clotting process and by storage. Therefore stored plasma, stored blood and in particular serum appear to provide more effective sources of the deficient factor than does fresh plasma, as

stressed by Aggeler, White et al.^{3,28} and by Biggs et al.⁶ Patients with PTA deficiency can probably undergo operative procedures satisfactorily provided precautions are taken to minimize blood loss and to replace the deficient clotting factor. In AHG deficiency, however,

picture of hemophilia raises new problems. A number of suggestions have been offered. Biggs et al.⁶ have proposed that the designation, hemophilia, be reserved for AHG deficiency and have applied the name "Christmas disease" to PTC deficiency.³ Brinkhous³⁰ has also suggested that

TABLE IX
SUMMARY OF CLINICAL AND CLOTTING CHARACTERISTICS OF AHG, PTC AND PTA DEFICIENCIES

	Anti-Hemophilic Globulin (AHG) Deficiency	Plasma Thromboplastin Component (PTC) Deficiency	Plasma Thromboplastin Antecedent (PTA) Deficiency
Sex	Male (female very rarely)	Male	Male and female
Hereditary pattern	Sex-linked, recessive trait carried by female, transmitted to male	Similar to AHG deficiency	Not sex-linked, transmitted to male and female by female and probably male carriers
Pattern of hemorrhage: Degree Sites	Depends upon clotting time and the degree of the clotting defect		
	Slight to very severe Joints frequent, follows trauma and any operative procedure	Slight to moderately severe Joints sometimes involved, follows trauma and operative procedures	Slight to moderate Joints rarely involved, most usually follows minor surgical procedures as tonsillectomy, tooth extraction
Clotting time	Normal to over 1 hour	Normal to about 60 minutes	Normal to 30 minutes
Clotting defect corrected by:			
Normal plasma	Yes	Yes	Yes
Normal BaSO ₄ -treated plasma	Yes	No	Yes
Normal serum	No	Yes	Yes
Fraction I	Yes	No	No
Normal BaSO ₄ -treated serum	No	No	Yes
Other Findings	Normal values—platelet count, prothrombin time, clot retraction Usually normal—bleeding time, tourniquet test Abnormal (degree related to the extent of the deficiency)—heparin clotting time, serum prothrombin time, recalcified clotting time of slowly and rapidly centrifuged plasma, thromboplastin generation		

operative procedures must be avoided if at all possible. Fraction 1, which has been effective in AHG deficiency, does not contain PTC³ or PTA.²²

Thus the importance of identification of the specific clotting abnormality in hemophilia-like diseases is apparent. Specific diagnosis is essential for the use of effective replacement therapy and for proper precautionary measures for these patients. Serious consequences may follow even minor surgical procedures in patients with slight, unrecognized PTA or PTC deficiencies.

The terminology for the increasing number of clotting defects which can give the clinical

hemophilia be used for AHG deficiency and has proposed a series of designations, "hemophiloid" A, B, C, etc., for PTC, PTA, labile and stable factor deficiencies. Soulier and Larrieu²⁴ and Cramer et al.³¹ have suggested the terms hemophilia A and B for AHG and PTC deficiencies, respectively. It is now strongly urged that the use of a common descriptive term for both a clotting factor and its concomitant deficiency would provide the simplest and least confusing terminology. The broad designation, hemophilia, would apply to a deficiency in a plasma thromboplastin factor, which could then be specified as AHG, PTC or PTA deficiency.

SUMMARY

1. Clinical and coagulation studies were performed in 33 patients with hemophilia-like diseases caused by deficiencies of anti-hemophilic globulin (AHG), plasma thromboplastin component (PTC) and plasma thromboplastin antecedent (PTA). Eleven carriers were similarly studied.

2. AHG and PTC deficiencies are transmitted as sex-linked recessive traits by the female to the male. PTA deficiency, on the other hand, is transmitted by either sex to both male and female children. A few carriers of mild AHG, PTC and PTA deficiencies exhibited slight bleeding tendencies and clotting defects.

3. The hemorrhagic manifestations were most severe in AHG deficiency, were moderate in PTC deficiency and mildest in PTA deficiency. Joint involvement and hematuria were predominant in AHG deficiency and rare in PTA deficiency. The severity of bleeding was generally related to the degree of prolongation of clotting time for each type of defect.

4. AHG deficiency was more frequently found in patients with clotting times above thirty minutes whereas PTC and PTA deficiencies were more common in patients with values below thirty minutes and in the normal range.

5. Evaluation of the sensitivity of various clotting tests in the diagnosis of hemophilia-like diseases reveals that the clotting time is a relatively insensitive criterion in mild cases; the clotting time of rapidly centrifuged, platelet-poor recalcified plasma is a moderately sensitive indicator; the heparin clotting time and rate of prothrombin utilization are relatively sensitive. However, matching or mixing studies are essential for identification of the type of defect.

6. A nomenclature for hemophilia and hemophilia-like diseases caused by a defect in a plasma thromboplastin factor is proposed. It is recommended that the terms anti-hemophilic globulin (AHG), plasma thromboplastin component (PTC) and plasma thromboplastin antecedent (PTA) be employed to designate both the clotting factors and their respective clinical deficiencies.

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Seminars on Antihypertensive Drugs

Pharmacology of Antihypertensive Drugs*

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FUNDAMENTAL FUNCTIONAL DISTURBANCES IN HYPERTENSION

A. Importance of Peripheral Resistance

ELEVATION of arterial pressure can be produced either by an increased cardiac output or an increased peripheral resistance to flow from the aorta into the venous system. It is generally agreed that, with the possible exception of pheochromocytoma, the cardiac output is within normal limits in patients suffering from hypertension and in animals in which hypertension has been induced experimentally. Therefore, it appears that the primary factor is an increase in the resistance to flow. This resistance is often spoken of as the total peripheral resistance (TPR). It is related to the resistance to flow in individual vascular beds R_1 , R_2 , etc., as:

$$\frac{1}{\text{TPR}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} \text{ etc.}$$

B. Factors Affecting Peripheral Resistance

Increased resistance to flow, in many cases, is due to increased tone of the vessels controlling flow (terminal arteries, arterioles and precapillary sphincters) since it is often reversible. However, structural changes resulting in narrowing of the lumen of these vessels may also play a part; this may be in the form of widespread thickening of the intima and hypertrophy of the muscle layer of the arterioles. Recently it has been postulated that the lumen may also be narrowed by migration of water and salts into the wall of the arterioles. Augmented resistance to flow could also be produced by increase in the viscosity of the blood, but such changes have not been noted. The increased resistance is associated with an elevation of the "critical closing pressure."¹

C. A Partial Rationale of the Hypertensive State

In any given organ the blood flow is dependent (1) upon the resistance to flow through the terminal arteries, etc., of the blood vessels supplying this organ and (2) upon the level of arterial pressure. Ordinarily the arterial pressure is maintained constant by the homeostatic regulatory mechanisms, i.e., the carotid sinus and aortic pressoreceptors and the vasomotor center. Fluctuating needs for blood flow, due to variations in the metabolism, are met by local autoregulation of the vascular resistance, i.e., of the tone of the terminal arteries, arterioles and precapillary sphincters in the organ. However, under certain circumstances there may be partial obstruction of the supplying artery, or unusual resistance to flow in the regulating arteries of the organ. Under these circumstances, either the organ will suffer ischemia and possible death of the cells, as in the case of angina pectoris or myocardial infarction, or the organ may induce a change in the systemic circuit which raises systemic arterial pressure (produces hypertension) and thus restores the blood flow in the organ toward normal.

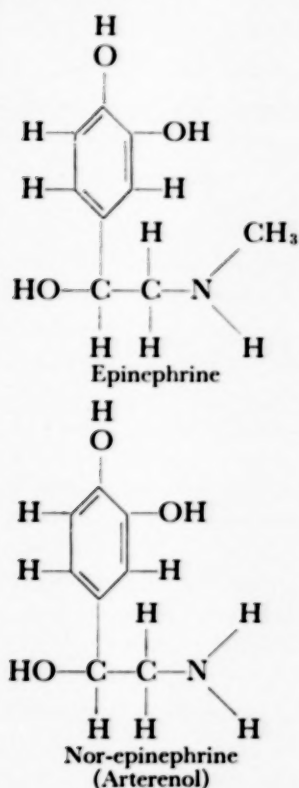
This compensatory type of phenomenon has been shown to be responsible for certain forms of hypertension due to interference with renal blood flow in experimental animals, and probably plays at least a contributory role in many if not most cases of human hypertension. It is possible, though not proven, that interference with the blood flow in organs other than the kidney might also induce such compensatory hypertension.

D. Mechanisms by Which Tone of Blood Vessels Which Control Total Peripheral Resistance Could Be Increased

1. *Increased Sympathetic or Adrenergic Activity.*
The generalized increased peripheral vascular

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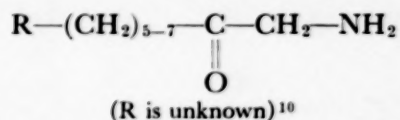
tone responsible for the hypertension may be due to augmentation of the normal sympathetic nervous system vasoconstrictor activity, especially in instances of neurogenic or psychogenic hypertension. Such overactivity is probably present in the temporary hypertension which can be produced in animals by stimulation of the cerebral cortex.² Excesses of sympathetic vasoconstrictor mediators, epinephrine and nor-epinephrine, may be present in hypertension associated with tumors of the adrenal medulla. The structural formula for these two sympathomimetic substances are:



2. Non-sympathomimetic Constrictor Substances.

A large number of circulating non-sympathomimetic constrictor substances have been suggested as the causative or contributing agent in many forms of experimental and human hypertension. Included among these hypothetical constrictor substances are: renin which reacts with hypertensinogen in the plasma to form hypertensin, angiotonin;³⁻⁶ vasoexcitor material, VEM;⁷ sustained pressor principle;⁸ cerebral vasopressor principle;⁹ pherentasin;¹⁰ nephirin, prolonged urinary pressor substance and nicotine-like bases¹⁰ and plasma vasoconstrictor factor.¹¹ Most of these are found in association with, and several are known to be formed by

partially ischemic kidneys. Ischemia of other vascular beds might also result in release of constrictor substances but the renal mechanism is the most clearly established. The structural formula for pherentasin is believed to be:



3. *Kidneys.* Renal ischemia, sufficient to cause formation of one or more of these constrictor substances, may occur with disease of the renal arteries or could result from repeated temporary or sustained renal arteriolar constriction due to overactivity of the sympathetic vasoconstrictor nerves or possibly to circulating constrictor substances. Alterations in intrarenal metabolism may also play a part.

4. *Adrenal Glands.* Hypertension also appears to be dependent upon a normally functioning adrenal cortex and may in certain cases result from an absolute or a relative increase in an adrenocortical salt-retaining hormone,^{10,12} especially in the presence of renin.¹³ It also appears to be dependent upon a certain minimum dietary intake of salt.¹⁴

5. *Carotid Sinus and Aortic Arch Pressoreceptors.* Ordinarily with elevation of arterial pressure the pressoreceptors of the carotid sinuses and aortic arch are excited, resulting in reflexly induced bradycardia and peripheral vasodilation. With the exception of experimental neurogenic hypertension, in which these buffer areas are denervated, and cases of pheochromocytoma which may be accompanied by tachycardia, the heart rate and sensitivity of the carotid sinus to application of external pressure are usually within normal limits. These findings would suggest that the pressoreceptors have been reset, possibly by the process of adaptation, to operate at the elevated arterial pressure level in a manner similar to that which they would ordinarily at normal levels of arterial pressure.

E. Possible Etiologic Factors

It is not the role of this communication to discuss in detail the etiology of hypertension but for orientation some of the agents which have been considered will be listed. These include: hereditary predisposition (it is said that, if both parents have hypertension, one's chances of having hypertension are around 45 per cent whereas they are only 3 per cent if neither parent has

hypertension); age (the incidence increases rapidly with age); environmental influences (hypertension appears to be more common in those living in Western civilization); emotions and personality (personality factors such as "subnormal assertiveness" and "obsessive-compulsive traits" are said to lead often to nervous tension; these may contribute to vascular hypertension but may also be induced by the hypertension); mechanical or chemical interference with renal circulation or metabolism (such as arteriosclerosis of the renal arteries, renal arteriolar nephrosclerosis and renal parenchymal disease—glomerulonephritis, pyelonephritis); endocrine disturbances (pheochromocytoma); and vascular deformities (such as coarctation of the aorta).¹⁰

F. Complications Accompanying Hypertension

Moderate hypertension *per se* is of no consequence and is often well tolerated for years. However, at times the hypertension seems to set up a vicious cycle tending ultimately to further elevation of pressure. Severe functional disturbances may accompany or result from prolonged hypertension, especially if the pressure becomes excessively elevated. These include headaches, angina pectoris, retinal hemorrhages or exudate, and renal insufficiency, as manifested by azotemia, reduced phenolphthalein excretion, and appearance of albumin and red cells in the urine. These secondary disturbances may be related to localized areas of vasoconstriction which are out of proportion to the elevation of arterial pressure and may therefore lead to localized ischemia. Such phenomena are particularly likely to occur during the malignant phase of hypertension. Hypertension also aggravates any existing tendency to atherosclerotic changes in the systemic arteries and contributes to left ventricular failure by increasing the work load of the heart.

POSSIBLE MECHANISMS FOR LOWERING THE HYPERTENSIVE ARTERIAL PRESSURE

Lowering the systemic arterial pressure may impair the blood flow in some organs but this may be balanced by a reduced load on the body as a whole, and occasionally the cycle of events maintaining the hypertension may be broken by restoring the arterial pressure to normal levels. Therefore, an attempt at lowering the hyper-

tension pressure is probably justified in most hypertensive patients.

On a hypothetical basis the elevated arterial pressure might be returned to normal levels by: (1) restoration of normal blood flow to any organ which is initiating hypertension as a means for compensating its own deficiency of circulation or (2) by directly interfering with the generalized vasoconstrictor mechanism responsible for the increased total peripheral resistance. The latter might be accomplished by: (a) interruption, suppression or blockade of autonomic vasoconstrictor impulses, (b) reduction in the concentration of, antagonism to, or blockade of the effects of circulating constrictor substances, (c) administration of vasodilator substances, (d) use of procedures which might reverse or prevent the hypertrophy, edema formation or other structural change in the blood vessels or (e) decreasing blood viscosity.

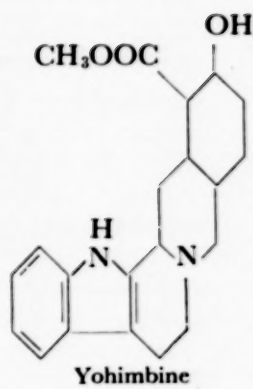
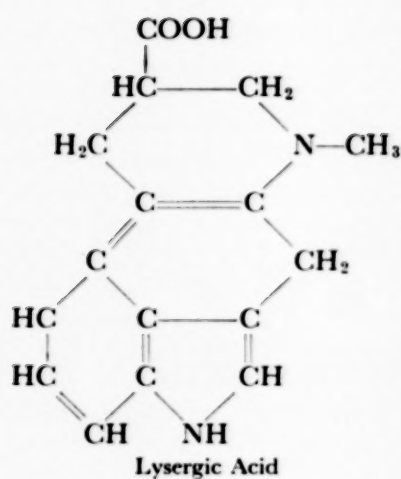
It is desirable that lowering of the arterial pressure be accomplished by a proportional decrease in the resistance in all vascular beds, and it is essential that the blood flow in vital regions such as the heart, central nervous system and kidneys not be reduced. Unfortunately, part of the lowering of arterial pressure accomplished by many hypotensive agents is due either to a decrease in cardiac output or to a lowering of the peripheral resistance in less vital areas. In either case this results in a decrease in flow to these vital regions. Because of this, good clinical judgment and careful observation are necessary to be sure that the lowering of the systemic arterial pressure is not accomplished at too great a cost to some particular organ system.

DRUGS CURRENTLY USED IN THE DIAGNOSIS AND TREATMENT OF HYPERTENSION

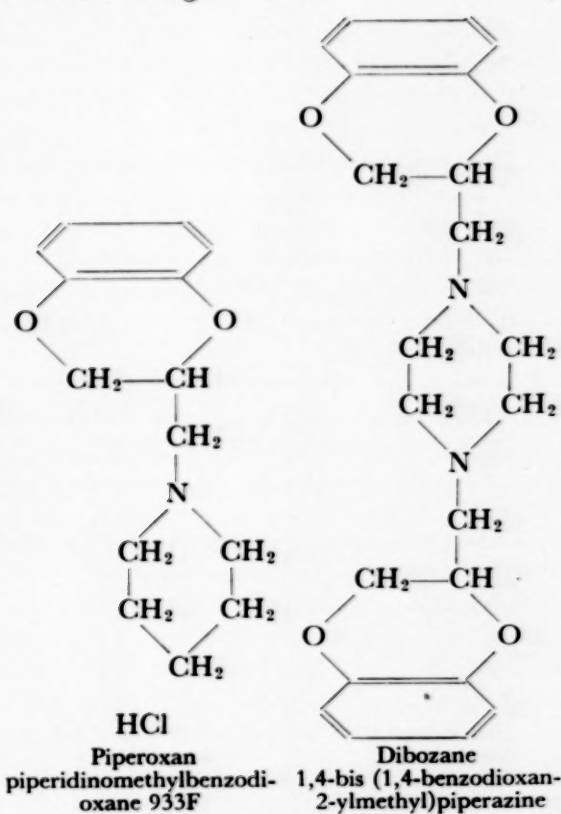
A large number of drugs have been used at one time or another in the treatment of hypertension. The following discussion will, however, be limited to a small group of drugs which are currently being most actively investigated or used in this field.

A. Adrenergic Blocking Drugs

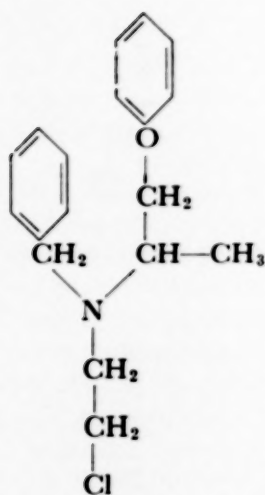
1. *Chemical Structure.* Much interest has been shown in this group of drugs and as a result a large number of synthetic compounds of this type are now available. These include:



Natural Compounds

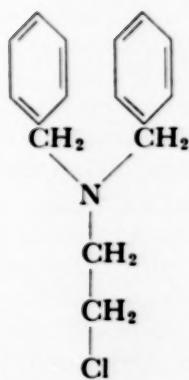


Dioxane Derivatives

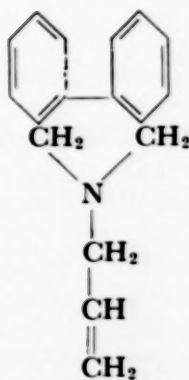


Dibenzyline
(N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride)

β-haloalkylamine Derivatives

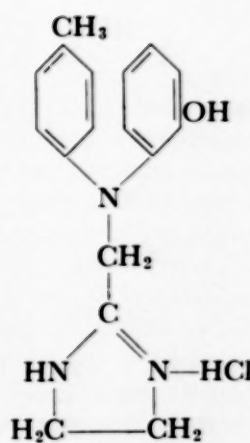


Dibenamine
N, N-dibenzyl-β-chloroethylamine hydrochloride



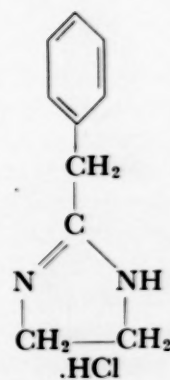
.H₃PO₃
Azapetine (Ilidar)
6-allyl-6,7-dihydro-5H-dibenz(c,e)azepine phosphate

Dibenzazepine Derivative



Phentolamine (Regitine)
2-([N-(m-Hydroxyphenyl)-p-toluidino]methyl)-2-imidazoline hydrochloride

Imidazoline Derivatives



Tolazoline (Priscoline)
2-benzyl-4,5-imidazoline hydrochloride

2. *Principal Pharmacologic Actions.* Except for minor differences all of the compounds have almost identical principal pharmacologic effects. The differences between them are principally variations in the dose required to produce a given effect and in the duration of the effect.

(a) *Receptor areas:* All of these compounds appear to attach themselves to the receptor areas of certain of the effector cells which are activated by either the sympathetic nervous system or circulating adrenergic substances. This attachment is quite firm and acts to prevent the adrenergic mediators from having access to the receptor areas. This blockade lessens or abolishes the customary response of the effector cells to adrenergic stimulation. The intensity of the blockade varies from one structure to another; in some structures blockade is complete at moderate doses; in others complete blockade is attained only after very large doses of the blocking drugs.¹⁵

(b) *Blockade of vasoconstrictor receptors:* The vasoconstrictor receptors of skin, skeletal muscle and intestine are readily activated by adrenergic stimulation by way of the sympathetic nerve impulses. These structures and the vasoconstrictors in the kidney are also activated by circulating sympathomimetic substances, such as L-epinephrine, L-nor-epinephrine and phenylephrine (neo-synephrine®). All of these vasoconstrictor responses are diminished by progressively increasing doses and finally blocked completely by moderate doses of the adrenergic blocking drugs.¹⁵⁻²¹ Adrenergic stimulation, either by way of the sympathetic nerve or by injection of sympathomimetic substances, has no vasoconstrictor action on the cardiac circulation;²² the responses in other areas are not well established.

(c) *Blockade of vasodilator receptors:* In the vasculature of skeletal muscle and of the splanchnic system L-epinephrine but not L-nor-epinephrine stimulates vasodilator receptors simultaneously with the vasoconstrictor receptors. Ordinarily the vasoconstrictor receptors are more potent and vasoconstriction is the customary response to intra-arterial injections of epinephrine. However, in some species and at some times the primary response is vasodilation. The vasodilator receptors are much less readily blocked than are the vasoconstrictors. As a consequence, small doses of the adrenergic blocking drugs block the vasoconstrictor receptors sufficiently to unmask the stimulation of the

vasodilator receptors. This results in conversion of the vasoconstrictor response to epinephrine to vasodilation, the so-called epinephrine reversal.²³

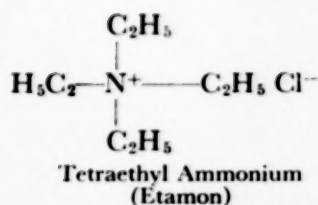
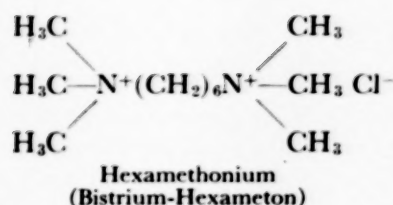
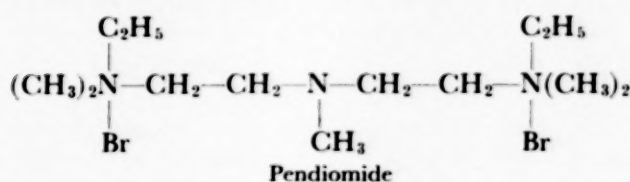
After moderate doses of the blocking drugs, sufficient to block completely the constrictor responses to adrenergic stimulation in skin, skeletal muscle and the splanchnic area, epinephrine still stimulates the vasodilator receptors in skeletal muscle. The vasodilator receptors are blocked only at very high doses of the blocking drugs.¹⁷

(d) *Basal vasomotor tone:* In most vascular beds the resting or basal sympathetic and adrenergically mediated vasoconstrictor tone is normally low. Therefore, the adrenergic blocking drugs *per se* will have little effect. However, in the skin of subjects exposed to a cool environment, vasomotor tone is high and vasodilation will accompany administration of these drugs.²⁴ Dibenzylamine,[®] ilidar[®] and phentolamine may reduce arterial pressure without depressing glomerular filtration rate or renal plasma flow significantly.²⁵

3. *Potential Clinical Usefulness.* The ability of small doses of the blocking drugs to unmask the vasodilator effects of epinephrine makes this group of drugs useful in detecting epinephrine-secreting pheochromocytomas. In the presence of such tumors small doses of any of the blocking drugs tend, by their epinephrine-reversing effect, to lower the hypertensive arterial pressure to hypotensive levels. In other forms of hypertension such doses have little effect on the elevated blood pressure. While ilidar, one of the newest members of this group, has not been studied from this point of view, its wide dose range between epinephrine reversal and nor-epinephrine blockade should make it a useful drug for the diagnosis and management of pheochromocytoma.

While moderate doses of the blocking drugs will block the vasoconstrictor responses to circulating L-nor-epinephrine and to sympathetic impulses, their usefulness as hypotensive agents in essential and other forms of hypertension is limited because of their tendency to cause postural hypotension and other untoward side effects. This may be due in part to the marked dilator responses induced in skeletal muscle and the splanchnic viscera by circulating epinephrine in the presence of such doses of the blocking drugs. At this level of blockade, circulating epinephrine does not cause vasodilation in such

vital areas as the kidney or heart and probably also not in the cerebral vasculature. The hypotension is probably in part due to decreased availability of blood in the central venous reservoir, due to peripheral pooling, since it is lessened by placing the heart in a dependent position relative particularly to the abdomen and lower extremities.

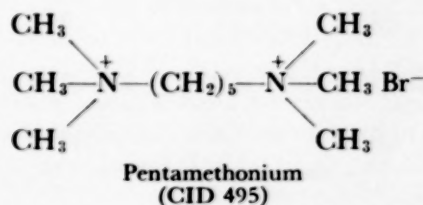
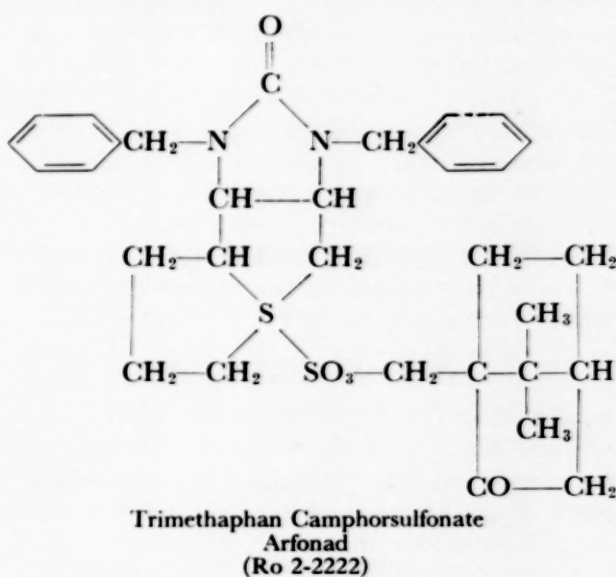


4. *Side Effects.* Besides postural hypotension, manifested by weakness, nausea, dizziness, tachycardia and palpitation, effective doses of various members of this drug group tend to cause nasal stuffiness, cutis anserina, chilliness, formication, lassitude, weakness, headache, gastrointestinal disturbances such as nausea, vomiting and abdominal distress, and occasionally drug fever or aggravation of any existing asthma or any difficulty in retaining urine in the bladder. The incidence and severity of the side effects varies markedly among the members of the drug group and from patient to patient.^{15,26,27} It is therefore necessary to choose for each particular patient that member of the group which causes the most satisfactory response with the least side effects. Because these drugs are less effective vasodilators in the vital than in the non-vital areas, they should be used with caution in pa-

tients with cerebral arteriosclerosis, or with coronary or renal insufficiency.

B. Ganglionic Blocking Drugs

1. *Chemical Structure.* A fairly large group of drugs possessing ganglionic blocking action are available. The structural formulas for the more common ones are:



2. *Principal Pharmacologic Actions.* (a) *Site of blockade:* The principal pharmacologic action of these drugs is exerted in the autonomic ganglia, both sympathetic and parasympathetic, at which site they block transmission at the synapse between the terminals of preganglionic fibers (white rami) and the dendrites of the ganglionic cells (which give rise to the postganglionic grey rami fibers).²⁸ The various ganglia vary considerably in their sensitivity to blockade, and complete blockade is rarely obtained even with quite large doses.²⁹ The blockade is a nicotine-like action. These drugs have no significant effect on the transmission to the effector cells of postganglionic impulses of either the sympathetic or parasympathetic systems, or on the action on the effector cells of either parasympathomimetic (acetylcholine) or sympathomimetic substances (epinephrine or nor-

epinephrine). In fact the vasopressor effects of the latter two are often accentuated during such ganglionic blockade.³⁰

(b) *Basal vasomotor tone:* As was mentioned under the adrenergic blocking drugs, the basal sympathetic vasomotor tone is normally low, and therefore moderate doses of these drugs *per se* will have little effect on the blood flow. In instances of cutaneous vasoconstriction due to cooling, these drugs are highly effective in causing vasodilation.³¹

(c) *Effects on renal blood flow:* In dogs hexamethonium appears to decrease mean arterial pressure and renal blood flow despite a slight decrease in renal vascular resistance although glomerular filtration is unchanged.³² With maintained lowering of hypertensive pressure, renal function may return toward normal if renal damage is not too severe.

(d) *Effects on cardiac output:* After an initial increase, cardiac output is decreased by hexamethonium. Peripheral resistance initially decreases, then returns toward or above normal as cardiac output falls.³³ During this phase cardiac work is reduced but myocardial oxygen consumption remains unchanged.³⁴

3. *Clinical Usefulness.* The antihypertensive effects of these substances are probably exerted by way of their blockade of the transmission of impulses through the sympathetic ganglia, thus decreasing total peripheral resistance. The important ones go to the vasoconstrictors in such regions as the skin, skeletal muscle and splanchnic viscera.

As noted above these drugs are reported to cause cerebral vasodilation though such vasodilation does not protect against cerebral hypoxia if the arterial pressure falls sufficiently to lower cerebral blood flow to or below 31.5 ml./min./100 gm. of brain tissue. This occurs at arterial pressures of 40 to 100 mm. Hg; the higher levels are in patients with malignant hypertension.³⁵

The sympathetic impulses going to the chronotropic and inotropic receptors of the heart are also blocked by these drugs, thus lowering the rate and more particularly the vigor of the ventricular contractions and tending to decrease cardiac output. As with the adrenergic blocking drugs, cardiac output also tends to be decreased due to peripheral pooling (decreased venous return).³⁶

Coronary vasodilation will not likely result but the reduction in the pressure work load and

the decreased myocardial stimulation, induced by blockade, may improve the ratio of coronary flow to myocardial oxygen consumption.

4. *Side Effects.* Side effects due to blockade of the sympathetic nervous paths include postural hypotension, redness of the eyes and nasal congestion. The principal side effects, however, are to be expected from blockade of the parasympathetic nervous system. These include blurring of vision due to loss of accommodation, dryness of the mouth, impaired sweating, anorexia and constipation bordering on ileus. Occasionally diarrhea, urinary retention and impotence may occur. As with the adrenergic blocking drugs, these agents should be used with caution in patients with cerebral arteriosclerosis, coronary or renal insufficiency.

Data on elimination are available only for tetraethyl ammonium, which is excreted unchanged by the kidney.

C. Reflexly Induced Depression of the Arterial Pressure, Veratrum Group of Drugs

For many years a group of drugs have been known which tend to cause bradycardia, depression of arterial pressure and respiratory slowing. The sources of these drugs are the roots and rhizomes of *Veratrum album* and *Veratrum viride*, and the seeds of *Schoenocaulon officinale*. From the *Veratrum* plants there have been obtained the crystalline alkaloids, protoveratrine, germerine, jervine, rubijervine, pseudojervine and veratrosine. The seeds of *Schoenocaulon officinale* yield the crystalline cevadine and the amorphous veratridine.

1. *Composition.* Some of the alkaloids are ester alkaloids and by hydrolysis these can be split into a basic moiety or alkamine, and one or more organic acids. For example, protoveratrine on hydrolysis yields protoverine and acetic acid, methylethyl acetic acid and methylethyl glycolic acid.³⁷ The alkamines are C₂₇ compounds and appear to be built upon a regular or modified sterole structure which is closely related to that of the aglycones of the cardiac glycosides.

Many of the original alkaloid extracts vary markedly in their composition from one batch to another. More recently, extracts with a much more constant composition have been prepared. Included among these is alkavervir (veriloid®), which is a mixture of constant composition of the alkaloids obtained by the selective extraction of *Veratrum viride* (NNR 1953). Another preparation of *veratrum viride* is vergitryl.®

Other recent preparations are mixtures of the pure crystalline protoveratrine A and B (veralba and provell maleate®). The potencies of the purified extracts are considerably greater than those of the crude extracts; and the potencies of the ester alkaloids are much greater than those of the alkamines.

2. Pharmacologic Actions. Three effects on the circulation of this group of drugs are distinguishable. The first is a depressor or hypotensive effect and the second is cardiac slowing; both of these occur with small doses of the veratrum alkaloids. The third can be observed only with large doses and is characterized by a pressor and cardioaccelerator effect. Other effects which have been noted in standardizing the drug and which might be classified as side effects are slowing of respiration, induction of emesis and alterations in the excitability of nerve and muscle. These latter non-circulatory effects will not be discussed further in this paper.

(a) *Cardiac slowing effect of small doses of the veratrum alkaloids:* Intravenous injection of small doses of the veratrum alkaloids in mammals leads to a reflexly induced cardiac slowing which is roughly proportional to the dose. When the injection is made close to the right atrium, the bradycardia begins within a few seconds and reaches its peak in a half to three minutes; its total effect lasts five to thirty minutes. The cardiac slowing is abolished by vagotomy or by large doses of atropine.

Perfusion experiments in which the head and the heart-lung regions were connected only by the nerves indicate that injection of these drugs into the heart-lung circuit causes a decrease in heart rate which is abolished when the vagi are cut. This indicates that the effect is produced by stimulation of sensory endings in the thorax, the Bezold effect. According to Dawes³⁸ this effect, the coronary "chemoreflex," is best obtained when the drug is injected into the circumflex coronary artery; he believes that the receptors are associated with the arterial supply to the left ventricle.

Protoveratrine injected into the isolated cerebral circulation also causes cardiac slowing which can still be obtained, though with lesser intensity, after denervation of the carotid sinus; this also is abolished or markedly reduced by vagal section, vagal cooling or administration of large doses of atropine.

These findings suggest that the reflexly induced cardiac slowing may arise from three

possible sites, one, intrathoracic receptors possibly in the region of the left ventricle; two, receptors in the region of the carotid sinus or carotid body; and three, intracranial receptors. Since the cardiac slowing is largely abolished by atropine or vagal section, the effect is probably due to increased activation of the vagal cardio-inhibitory fibers. However, some simultaneous decrease in the sympathetic cardioaccelerator impulses may also be responsible.³⁹

Swiss and Mason,⁴⁰ on the other hand, believe from cross circulation experiments similar to those above, that bradycardia induced by veriloid, protoveratrine, veratridine and veratramine is due only to their effects on receptors in the body of the animal and that when these substances are confined to the head they are without effect on the heart rate.

(b) *Vasodepressor effect:* The vasodepressor effect is characterized by a decline in arterial pressure and increase in the blood flow into and in the volume of various organs, thus suggesting that it is due to a reflexly induced vasodilation. Most authors^{37,39,40} are in agreement that a hypotensive reaction can be induced by injection of these drugs either into the body, presumably eliciting the coronary "chemoreflex," or into the isolated head.

The vasodilator response is not due to blockade of the effector cells since these respond normally to constrictor substances such as epinephrine and pituitary extract, and to reflexly induced phenomena such as asphyxia. The vasodilator action is not due to a direct effect on the blood vessels since intra-arterial injection of comparable doses has no significant effect on blood flow in various vascular beds. Goth, Harrison, and Blackmore⁴¹ report that after veralba administration in chloralose-urethane anesthetized dogs, histamine and methacholine produce a more marked fall and epinephrine a more marked rise in arterial pressure than in control animals. They suggest the possibility of a direct peripheral effect of the vessels; it would appear more likely, however, that this effect is due to depression of the actions of the buffer mechanisms (carotid sinuses).

The hypotensive response to the veratrum drugs is not abolished by administration of atropine although this drug does abolish the bradycardia. Interruption of the conductivity of the vagus nerve by cooling blocks the effect of these drugs when they are injected into the coronary artery or the atria, particularly into

the isolated head—heart-lung preparation. Vagal section diminishes, presumably by abolishing the bradycardia component, but does not abolish the hypotensive response to intravenous injection of these drugs in the whole animal.

According to Swiss and Mason,⁴⁰ when veratrum is confined to the body of the dog, hypotension is seen only as a concomitant of bradycardia, and prevention of the bradycardia abolishes the hypotension. They find that veriloid, protoveratrine, veratridine and veratrimine, when confined to the head of the dog with carotids innervated and vagi intact, produces only hypotension without alteration in heart rate. This hypotension is still evoked by each derivative after atropine or vagotomy, and is not decreased by carotid denervation. They concluded that this central action appears to be the more important mechanism in the clinical effectiveness of this group of drugs. On the other hand, Gruhzit, Freyburger and Moe⁴² found that vagotomy plus denervation of the carotid sinus pressoreceptors (without destruction of the chemoreceptors) completely prevents the depressor response to veriloid. They believe that the drug causes hypotension by sensitization of the stretch receptors (of the carotid sinus) rather than by facilitation of the central components of the reflex arc. Moran, Perkins and Richardson⁴³ believe that andromedotoxin, which has properties strikingly similar to the veratrum alkaloids, also acts by stimulating reflex vasodilation by way of either the carotid sinuses or bodies.

Wang, Ngai and Grossman⁴⁴ report that minute doses of protoveratrine, but not veratridine or veratrimine, injected into the adventitia of the common carotid bifurcation caused systemic hypotension and reduced carotid sinus pressoreponses, although the latter two caused hypotension when injected intravenously, even in debuffed animals. They concluded that veriloid, protoveratrine, germetrine, neogermetrine and germerine cause hypotension in vagotomized animals due largely to stimulation of the carotid sinus receptors, while veratridine and veratrimine cause hypotension largely by depression of the central vasomotor mechanism.

(c) *The cardioaccelerator and vasopressor effects:* Large doses of these drugs appear to cause cardiac acceleration, possibly through block of the vagal endings. The rise in pressure is due in part to vasoconstriction which appears to be a local action of the veratrum alkaloids on the blood vessel walls and possibly also to the effect

of the veratrum alkaloids on the central nervous system, leading to central vasomotor stimulation, or to the stimulation by the veratrum alkaloids of the release of vasoconstrictor substances such as epinephrine. These latter effects, however, are observed only with doses considerably above the ordinary clinical dosage level.⁴⁵

(d) *Renal function:* In dogs Nungesser and Hiatt⁴⁶ note no difference between the control renal hemodynamics of the innervated and denervated kidney. Lowering of the arterial pressure by veratrum decreases renal plasma flow and glomerular pressure equally in the innervated and denervated kidney. They conclude that the renal circulation does not participate in the generalized vasodilation which is partly responsible for the depressor effect of veratrum.

3. *Methods for Standardization.* This group of drugs has been standardized on the basis (1) of their ability to induce hypotension in pentobarbital anesthetized dogs following intravenous administration;^{47,48} (2) their ability to depress the rise of pressure that normally follows occlusion of the carotid arteries; and (3) their ability to induce emesis. In recent studies it was reported that it was not possible to dissociate quantitatively the emetic from the hypotensive potencies of veralba, unitensin and protoveratrine A.⁴⁰

Data are not available on the mechanism or route of destruction or elimination of these drugs.

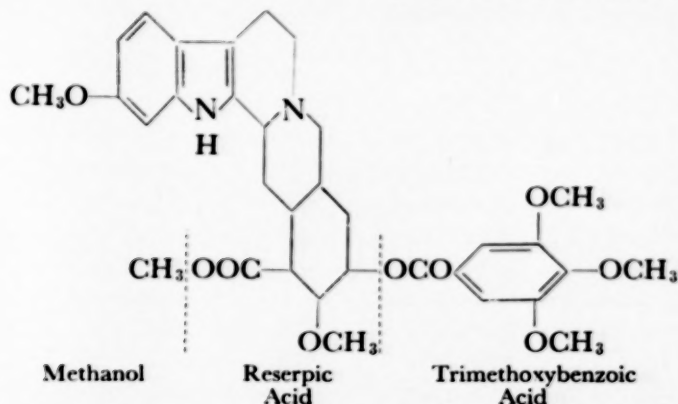
4. *Side Effects.* This group of drugs may be given orally, intravenously or intramuscularly. The greatest care, of course, must be used with the intravenous route. Overdosage results in severe postural hypotension and, particularly in the presence of digitalis, the patient may experience nausea, bradycardia and cardiac arrhythmias. The latter two may be alleviated by the use of 1 mg. of atropine given parenterally, and the hypotension may be counteracted by vasopressor substances such as ephedrine or phenylephrine (neo-synephrine).

D. Depressant Drugs (*Rauwolfia* Group)

There are some forty varieties of *Rauwolfia*, the most important of these being *Rauwolfia serpentina*. For centuries, extracts from the roots and leaves of *Rauwolfia serpentina* have been used in Indian medicine as a hypnotic, as a sedative in psychoses accompanied by states of excitation or tension, and in epilepsy. Since these extracts seemed also to be useful in the

treatment of hypertension,⁵⁰ several companies in this country became interested in the preparation of extracts of the crude drug, and also of highly purified extracts of its active principles.

1. *Available Preparations.* A preparation of the whole powdered root of *Rauwolfia serpentina* Benth is available under the trade name of raudixin.[®] This preparation contains $\frac{1}{2}$ unit, i.e., an amount of the root extract which is equal in hypotensive and adrenolytic potency to 50 mg. of a provisional reference standard (1 unit = 100 mg.) Rauwiloid[®] is a semi-purified extract of the alseroxylon fraction of *Rauwolfia serpentina* which is standardized on the basis of its effectiveness in producing a decline in arterial pressure, bradycardia and sedation. Reserpine, a purified crystalline extract of *Rauwolfia serpentina*, is available as serpasil. Recent studies⁵¹ indicate that its structural formula is:



Reserpine seems to exert all of the principal pharmacologic effects of the whole root, i.e., depression of arterial pressure, bradycardia and sedation.

Other alkaloids such as serpentine, serpentinine, ajmaline, ajmalicine and alkaloid G have shown no potency in doses up to 20 to 60 times that of effective doses of reserpine.⁵² The basic structure of reserpate acid is quite similar to that of yohimbine, but the activity lies in the whole ester since neither the reserpate acid nor the trimethoxybenzoic acid moieties exert significant sedative or hypotensive effects.⁵³ The effective dose is about 1/1000th that of the crude drug.

2. *Principal Pharmacological Actions.* (a) *Tranquilizing effects:* One prominent effect of the principal alkaloid group of substances is its tranquilizing action. It does not, however, depress the cerebral cortex as do the barbiturates; it does not alter significantly the electroencephalo-

gram;⁵⁴ it does not prevent metrazol- or picrotoxin-induced convulsions and even after fairly large doses patients and animals are not anesthetized but are readily aroused.^{55,56} Hyperdynamic patients find a decreased drive and do not "blow their tops" so readily while taking the drug. They may sleep more soundly at night and may drop off to sleep if sitting quietly, yet are usually capable of carrying on without difficulty their customary activities.

(b) *Induction of hypotension and bradycardia:* The hypotensive effect of reserpine is quite moderate in normal animals and has a rather flat dose response curve, in that the blood pressure declines to a moderate level with small doses and does not drop further even with quite large doses. It does not cause any fall of pressure in spinal animals. Reserpine causes slowing of the heart, which is partially prevented by atropine, but does not reduce cardiac output or stroke volume

output, and has no significant effect on coronary blood flow. It will also reduce tachycardia caused by hydrazinophthalazine.

(c) *Lack of adrenergic or ganglionic blockade:* Rauwiloid does not prevent the rise in arterial pressure induced by injections of epinephrine, or nor-epinephrine, or by stimulation of the splanchnic nerve, in fact the pressor response to epinephrine may be augmented.⁵⁷ It therefore does not exert any adrenergic blockade, at least in usual doses. It does not block the response to preganglionic stimulation of the sympathetic supply to the nictitating membrane and therefore does not exert any ganglionic blockade.⁵⁶

(d) *Non-sympathomimetic substances:* Reserpine does not block the pressor response to angiotonin, pherentasin or cerebral pressor substance. It does prevent vasospasm due to intra-arterial barium chloride but only at doses well above those used therapeutically. Rauwiloid does not

alter the hypotensive responses to acetylcholine or histamine.⁵⁷

(e) *Blockade of central and reflexly induced responses:* Reserpine blocks or reduces the rise in pressure induced by central stimulation of the sciatic or of the vagus nerves, or by lowering of the pressure in the carotid sinus by carotid occlusion.⁵⁸ It does not alter the response in the cold pressor test but does decrease the digital vasoconstrictor inspiratory reflex.⁵⁹ Rauwiloid blocks the blood pressure response to hypoxia (breathing 100 per cent nitrogen for forty-five seconds).⁵⁷

Reserpine causes miosis and relaxation of the nictitating membrane in intact dogs, suggesting decreased activity of the central sympathetic nervous system. It also causes ptosis which closely parallels the hypotensive effects; this property has proven useful in following separation procedures.⁶⁰ It also causes mild hypothermia but will not prevent or lower fever due to pyrogens or infections.⁵⁶

(f) *Renal function:* The decrease in arterial pressure in both normal and hypertensive men is not accompanied by a reduction in renal hemodynamics or water or electrolyte excretion, thus suggesting that renal vascular resistance decreases.⁶¹ The last effect could be due to the autoregulatory mechanisms in the kidney.

(g) *Endocrine activity:* Reserpine does not affect significantly the antidiuretic function of the posterior pituitary, or the production of androgens. In animals it reduces the frequency of cornified vaginal smears and reduces fertility⁶² but does not interfere with ovulation or basal temperatures in normal women.⁶³ The drug does not block the normal fall in eosinophil count in response to ACTH.⁵⁹

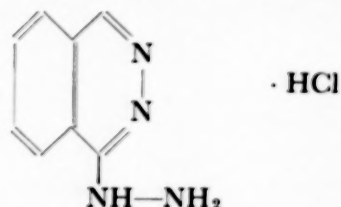
3. *Side Effects.* The LD₅₀ is extremely high compared to therapeutic doses. It is estimated to be the equivalent of around 280 mg. intravenously in man. Reserpine causes diarrhea in dogs, but this is not of importance in man. Agranulocytosis has not been encountered upon prolonged administration. Postural hypotension may occur with intravenous administration of the drug⁶⁴ but in customary therapeutic doses is less troublesome than with effective doses of the adrenergic or ganglionic blocking drugs. The principal distressing side effects are lethargy and difficulty in "getting going," decreased libido, a tendency to gain weight, and mild to severe nasal stuffiness which is said to be a histaminic effect and to be relieved by anti-

histaminics.⁶⁵ However, it has been my experience that the nasal stuffiness is not readily relieved by antihistaminics or vasoconstrictors. It is said that, in excessive doses, it causes nightmares or agitated depression⁶⁶ though I have not observed this in patients I have seen. In experimental animals reserpine exerts a peripheral cholinergic type of activity on the gastrointestinal tract.⁶⁷

Unlike most other hypotensive drugs, the effects come on only gradually due presumably to an accumulative effect of repeated doses. The drug is almost as effective orally as it is intravenously. Nothing is known about the mechanism of its destruction or elimination.

E. 1-Hydrozinophthalazine (Hydralazine Hydrochloride)

1. *Structural Formula.* This drug, available under the trade name of apresoline® hydrochloride, has the following structural formula:



2. *Pharmacologic Actions.* Schroeder¹⁰ believes that the principal action of this substance is based upon the ability of the —NH₂ group of this compound to combine with the oxygen of

the carbonyl group O=C of pherentasin, resulting in loss of vasoactivity of the latter substance. He also notes that the substance has a strong affinity for heavy metals and combines loosely and reversibly with sulfhydryl-containing compounds.

The pressor effect of many primary amines is abolished by hydralazine. According to Schroeder,¹⁰ the pressor effect of serotonin is increased whereas Yonkman⁶⁸ believes that it is antagonized by hydralazine. Hydralazine weakly antagonizes the vasoconstrictor effect of epinephrine and nor-epinephrine, the cerebral vasoconstrictor substance⁹ and to some extent, angiotonin and hypertensin;^{13,68,69} but, since it does not reverse the pressor effects of epinephrine, it can hardly be classed as a true adrenergic blocking drug.

In unanesthetized dogs this drug stimulates the heart and increases the cardiac output, an

effect which can be prevented by the prior administration of hexamethonium.⁷⁰ These authors believe that the cardiac effects of hydralazine may be central in origin and mediated over the sympathetic nervous system. Other investigators⁷¹ believe that they have demonstrated that hydralazine exerts a direct dilator effect on the blood vessels of sympathectomized extremities.

The substance tends to lower arterial pressure without decreasing renal plasma flow and in fact may even increase the flow. This effect is not prevented by the prior administration of hexamethonium.⁷⁰

3. Side Effects. The most important side effect of hydralazine is headache. It may be lessened by use of small initial doses and by the simultaneous administration of an antihistamine. The drug is said to inhibit the action of histaminase. A syndrome simulating collagen disease may be seen during prolonged administration.⁷² Tachycardia and palpitation are significant side effects. Postural hypotension and circulatory collapse are rarely seen. In patients with coronary disease evidence of myocardial ischemia, as indicated by angina, may occur in association with the use of hydralazine, even if hypotension does not occur. When hydralazine and hexamethonium are used together, postural hypotension may occur and increase the tendency for myocardial ischemia.⁶⁶

F. Renin and Antirenin

Wakerlin and his associates have been studying the effects of actively and passively induced antirenins on renal hypertension for a number of years but the studies have not yet progressed to the point where they may be applied to the treatment of human hypertension.^{73,74}

CONCLUSIONS

A large group of antihypertensive drugs with diverse actions is described. Any one of these may prove useful in a variety of types of hypertension. Many of them used in combination seem to exert a synergistic effect. This is particularly true of the heart rate which tends (1) to be increased by the adrenergic blocking drugs and by hydralazine and (2) to be depressed by the ganglionic blocking drugs and the veratrum group. In this respect a combination of a drug from (1) and one from (2) would be advantageous. However, the dose of each drug should be adjusted to the needs and the sensitivity to

side effects of the particular patient. Because of this the author decries the tendency of many drug firms to put out fixed combinations of these drugs.

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Clinic on Psychosomatic Problems

A Case of Arrested Rheumatic Heart Disease with Severe Neurosis Mistaken for "Ulcerative Colitis"

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric Services of the Massachusetts General Hospital. This psychiatric conference was edited by Dr. Stanley Cobb.

DR. FRANK K. AUSTEN: This is the second admission to Massachusetts General Hospital of this thirty year old, twice married mother of two. She entered the medical wards one month before because of rectal bleeding eleven days and again two hours prior to admission. After two weeks the medical work-up was completed. The patient, who had been experiencing "strange sensations" for ten weeks, then said she desired psychiatric aid. She was transferred to the Psychiatric Ward with the diagnoses of rheumatic heart disease (? active), ? early ulcerative colitis and anxiety neurosis.

The patient was apparently well until twenty years ago, at the age of ten, when the diagnosis of rheumatic heart disease was made. This was based on a history of scarlet fever and the physical signs of cardiac enlargement, mitral regurgitation and stenosis. Nine months later the patient was admitted to Massachusetts General Hospital with a diagnosis of rheumatic heart disease, subacute activity, decompensation and secondary anemia, and shortly thereafter was transferred to the House of the Good Samaritan where she remained for a year and a half. After that she was well, with the exception of an exacerbation requiring six months' convalescence at the age of fifteen. She married and had two uneventful pregnancies. A year and a half ago low-grade fever, joint pains and an aching back developed. Nine months ago, because of persistence of symptoms, she underwent a tonsillectomy and sinus drainage. The symptoms persisted, and seven months ago she was given cortisone by her private physician. Six months ago "ovarian hormone" injections were introduced because of scanty menses. Both endocrine

therapies were discontinued three months prior to admission.

Two and a half months ago, while her husband was entertaining at a summer resort, she suddenly experienced a "strange sensation." This spread out over her body from the lower abdomen and genital region and was described as tingling, vibrating or possibly sexual in nature. Such episodes increased in intensity and frequency until finally the patient refused to leave the house.

About two months ago, because of persistence of the low-grade fever, malaise and arthralgia, and because of the development of the "strange sensations," the patient consented to treatment at her mother's house. The initial therapeutic regimen included complete bed rest, aspirin, oral penicillin, aureomycin troches and phenobarbital. Later all oral antibiotics were discontinued and parenteral penicillin and streptomycin instituted. Her physician believed the "strange sensations" were a consequence of the endocrine therapy and recommended sexual abstinence.

Eleven days prior to admission, two weeks after discontinuation of oral antibiotics and about one hour after a nicotinic acid flush, the patient experienced an episode of rectal bleeding. She had several attacks of bloody diarrhea accompanied by abdominal cramps. After one of these attacks she fainted. Within two days the stools cleared, but again six hours prior to admission the bleeding recurred. The "strange sensations" which had diminished in frequency and intensity were aggravated by the bleeding and became almost continuous.

She was admitted to the Medical Ward with a

diagnosis of ulcerative colitis and rheumatic exacerbation. Sigmoidoscopic and barium enema examinations were unremarkable, though some observers believed that the mucosal changes of early ulcerative colitis were present. Evidence of rheumatic activity other than the elevated sedimentation rate and fever was not forthcoming, and thyroid studies were unremarkable. Therefore it seemed wise to transfer her to the Psychiatric Service for evaluation while awaiting further medical developments.

The past medical history included tonsillectomies, twenty years and nine months ago, uneventful deliveries eleven and six years ago, drainage of a pilonidal sinus eleven years ago and chicken pox nine years ago.

The patient, who was born in Boston, had few memories of her early life. She recalled that her parents fought a great deal and because they considered her irritable, moody and complaining, the persistence and progression of symptoms eventuating in the diagnosis of rheumatic heart disease were ignored. During the years in bed convalescing, she became resentful of her mother's inconsistent affection and neglect. This feeling was aggravated after her father's departure when she was ten. At fifteen the patient, dissatisfied with her home life, ran away with a boy. Intercourse was unsuccessful and a pattern of masturbation was instituted. After being apprehended and returned home, she experienced an exacerbation of rheumatic activity, and while convalescing began to masturbate excessively. After finishing high school she worked for a while. Pregnancy at nineteen was followed by marriage. Following delivery of her son she joined her husband. Their adjustment was quite unsatisfactory and she left him twice in the first two years of their marriage. Furthermore, because of his preferences, they settled into a sexual pattern of the alternate masturbation of one by the other. Finally during the third year of their marriage, she became involved with another man and despite her husband's attempts at reconciliation, she obtained a divorce. Eight months later, already three months pregnant, she married again. As during the first pregnancy, whenever alone she felt the overwhelming urge to masturbate and did so despite her superstition that this would harm the child.

Life with her second spouse presented two immediate problems in that they were unable to work out a pattern of sexual behavior acceptable

to the patient, and were faced from the start with a borderline economic status. Although she appreciates her husband's kindness she resents his lack of forcefulness.

Physical examination on admission revealed a well nourished, well developed, slightly plump, attractive, alert, apprehensive white woman with marked mood swings and a desire to please. She had a heart rate of 100 to 120, low fever, a palpable thyroid gland, an enlarged heart and murmurs of aortic stenosis and regurgitation and mitral regurgitation.

The patient remained on the Psychiatric Ward for two and a half weeks during which time sixteen therapeutic interviews of an hour each took place. At first she was completely preoccupied with a detailed description of her sex life which she felt was the principal disturbing element. She described these events in a surprisingly detached and open manner. She came to the interviews quite dressed up and even made inquiries about the interviewers' romantic interests. She revealed a diffuse hostility encompassing everyone with whom she had been emotionally close, directed especially against her husband and mother. On rare occasions this hostility was directed toward the interviewer but always for only a moment near the end of the hour.

STAFF CONFERENCE

DR. STANLEY COBB: I have been seeing her here. Let me bring up some things on which I would like to have help. In the first place, she was referred as a case of ulcerative colitis and had had some rectal hemorrhages. Is that incidental? How much relationship is there to antibiotics? Second, what relationship has the neurosis to the long invalidism in youth, rheumatic fever and recent fever? Why was she anxious for psychiatric help?

DR. AUSTEN: The bloody diarrhea is probably not related to the antibiotics because they were discontinued two weeks before the bleeding.

DR. FRANKLIN CARTER: Did she really have bleeding?

DR. AUSTEN: Her mother reported it, too.

DR. COBB: The x-rays showed some ulcerations but they are not typical of ulcerative colitis. I still believe it was caused by the aureomycin. What did the psychologic examinations show?

DR. GERSHEN ROSENBLUM: The projective tests depict a woman whose attempt to employ a rigid, repressive defense in coping with her

impulses and the demands of the world upon her has resulted in a constriction of independent, creative thinking and marked emotional labile reactions. These characteristics are revealed in the record in terms of her immature vocabulary, her frequent egocentric references, her childish and conspicuous sexual naïveté and a blocking of thought processes in the face of emotionally charged material. The presence of free-floating anxiety as well as childish fears is conspicuously present in the record. In addition, there appears to be a preoccupation in the sexual sphere with hints of disturbed heterosexuality, especially frigidity.

DR. CARTER: Any information on her functioning as a wife and mother?

DR. AUSTEN: She is a good housekeeper and devoted to her children.

DR. ERICH LINDEMANN: In my interview with her she certainly spoke very readily in a rather child-like way and was quite body-conscious. She obviously has found a refuge here and is not eager to leave. She is a little tremulous and has other signs of autonomic instability. She was quite aware of being observed and conscious of the audience. That may be an important item.

DR. LEMOYNE WHITE: She has been a night club singer.

DR. NORMAN BERNSTEIN: In group therapy sessions she spoke up cheerfully and forcefully and kept the group going. She was always cheerful and talkative, often overtalkative. Most of the content was platitudes.

DR. GARDNER QUARTON: In the beginning we wanted to find out whether she had ulcerative colitis or something else. My opinion would be that she does not have this, medically or psychiatrically. Rather early we thought she had anxiety hysteria characterized by simplicity in her personality and by the freedom with which she brought out the sexual material, and the concern about masturbation. She enjoys interviews and has a joking manner as well as a serious questioning about things. Her father left at a critical time in her life, the beginning of adolescence, when she had concern about sexuality. She tried to relate to men and had three unsatisfactory relationships. At the time her relationship to father was weakest, her relationship with mother was bad too. She could not relate to her mother, who was more like an unsatisfactory sister to her. With all this she has done very well. She is not as sick as we might think she would be. Her ability to relate to the

doctor and ability to run a home indicate that she is getting along fairly well. Illnesses were a treat to her, bringing her back to childhood conflicts. They led her to be more afraid of illnesses than necessary. I think she should not stay here too long. The ward constitutes a defense that is difficult to work through. I think we should reassure her and continue seeing her outside. She can accept psychiatric help.

DR. LINDEMANN: Do you have any theories about the bleeding?

DR. QUARTON: We have to regard it as undiagnosed. Dr. Ellis does not attribute it to ulcerative colitis but thinks it is due to a hemorrhoid. There is not much reason for us to be too concerned. It concerns her and she gives it a sexual meaning, but I doubt if it is a result of masturbation.

DR. LINDEMANN: I do not know how many of you remember the early paper of Freud, when he was concerned about psychoneurosis and "actual" neurosis. Now we rarely seem to have a picture of free-floating anxiety, palpitation, body consciousness and autonomic disorders which he describes so well in "actual" neurosis and which he tied in with masturbation conflicts. It is not common now to have a central focus on masturbation. The cultural pattern has changed and conflicts are not so upsetting, except in young men tied in with passive homosexuality. Why does this happen in a young girl such as this? Why should she come in to get forgiveness? "I am a pretty bad girl; see what a masturbator I am." I thought there might be a mild mood disturbance due to the hypochondriacal affect and concentration upon sensations one can have after paying attention to them. She appears immature. In the face of the report, she says she is not doing well. I was interested in the encounter with her father. The question which is not clear is: is this an original personality-stunting in character with institutional experience and unfortunate contacts with parents? Does she have somewhere a more adequate mode of functioning than is apparent? I am inclined toward the latter. In the face of a traumatic event not yet fully understood, she took recourse to a good doctor, said she was a naughty girl and clings to the hospital. I agree that the technical problem is how long to permit her to use the hospital, and how much to help her solve her problems. There is an uncertainty about her sexual adjustment. There is no absence or repression of sexual awareness. She accepts sexuality as

something which is her just due, but wants another organization of sexual life which is more rewarding. It may have started with her poor relationship to her father and bewilderment about what went on between mother and father.

DR. WHITE: Isn't she more depressed than has been readily apparent? Sexuality is immature yet there is a striving for it.

DR. LINDEMANN: It is a reactive depression in a hysterical character rather than a disturbance of a cyclothymic type. Is it ulcerative colitis? None of us think so from the psychologic point of view. We agree it is a neurotic picture with hysterical, depressive trends.

As to treatment, there should be no protracted exploration. We should help her to have a balance between the need for care and her ability to face the issues. She already has an attachment to Dr. Austen. There is a problem of not getting more of that than can be handled. I recommend a shift of emphasis toward reviewing operations at home. What are her tasks? What is the burden to face at home? One should point out the resources. She is impoverished along social lines.

It would be worth while to get some help from social service and to get acquainted with the husband and brother and to obtain a more objective picture. The mother and husband have such distorted perceptions of what we are doing here. This could be clarified via the social worker. It is interesting how psychologic problems do border on ethical problems.

FOLLOW-UP

The patient improved during her hospitalization. The "strange sensations" decreased in intensity and frequency. On one occasion near the end of her hospitalization she was visited simultaneously by mother and husband; and since neither had any appreciation of the patient's problems and each held the other responsible, an anxiety attack was not an unexpected consequence. It was of particular interest, however, that in describing the event the patient failed to mention the "strange sensations," still present but now well tolerated, and related only to her new symptom of recurrent retching. Since she exhibited an increasing dependency on her hospitalization and a growing dissatisfaction with her reality situation, it seemed advisable to discharge her as soon as she evidenced any interest in returning home. This was carried out with the understanding that she

was to return to the Outpatient Department in three days and was to be followed in the Medical Clinic as well.

At the appointed time she telephoned to state that she was incapacitated by recurrent vomiting. She also failed to meet a second appointment and revealed that she had begun to take sedatives again. At last she came in. She was tense, anxious and discouraged because her husband was unemployed and because she had experienced a severe bout of vomiting while caring for one of her children on a trial basis. As the interview proceeded she relaxed, became more cheerful and formulated a plan whereby she would face her problems. Her most significant decision was to take back her children immediately rather than allow them to grow up with her relatives as her family had recommended.

She was seen again three months after discharge and exhibited considerable improvement in that both children were home, she was able to leave the house without becoming upset and the "strange sensations," though present at times, in no way disturbed her.

SUMMARY

This patient experienced a disturbed childhood in which there was little opportunity for the usual affectionate parent-child relationships. The development of a chronic illness, rheumatic heart disease, with subsequent prolonged periods of bed rest accentuated an infantile attitude, an immature approach to sexual matters, a feeling of tremendous insecurity and a marked hostility toward her family.

During the bulk of the interviews the patient was permitted to speak freely of whatever she wished. She talked excessively about sex matters. When it became apparent that she was fundamentally a person with strength of character, it seemed advisable to stop further probing. Instead a course of reassurance and explanation of material at the conscious level was instituted. In effect she was led to conclude that the "strange sensations" were of no importance and that she was completely adequate to handle her reality problems. She was discharged from the hospital before she became too dependent. She was then helped in the Outpatient Department to face her problems at home.

The psychiatric interviews helped her in several ways. The more obvious ones were: (1) Relieving her anxiety over the "strange feelings" by explaining them as harmless vasomotor

phenomena to be expected when fears about masturbation arose. (2) Talking to her as an adult worthy of respect. This includes not letting her become too dependent and flirtatious. (3) Steering the talks away from sex with which she was preoccupied. This made her learn that she could have a close relationship with a man (her therapist) without any risk of falling into her immature pattern of seduction and elopement. (4) When vomiting and retching were substituted as symptoms for the "strange feelings," paying little attention to them, and turning the interviews to her reality problems of home and job. (5) Giving her confidence by always being willing to listen and by repeatedly explaining her lack of confidence in herself on the basis of her childhood deprivations and invalidism.

The prognosis for the immediate future is good. She can continue to look after her family with occasional trips to the Outpatient Department for support of her morale. In the long view the inevitable break in cardiac compensation

will pose a serious medical problem complicated by the old neurosis which will doubtless recur at that time. Perhaps enough self-confidence can be built up in the intervening years to enable her to face this situation with courage and without regression to childhood patterns.

The "ulcerative colitis" for which she was admitted was, fortunately, a mistake in diagnosis. The bleeding in the colon was probably due to superficial ulceration caused by aureomycin. Her psychologic structure was not the one often found in patients with ulcerative colitis: deep depression and schizoid trends. True, she was mildly depressed but her reactions were "hysterical" in type, i.e., immature, regressive, dependent. She made use of symptoms to control her environment ("conversion"). She changed from one symptom to another. She had an actual sex problem that was unsolved at first and apparently led to feelings of guilt and anxiety. All this fits in with the diagnosis of neurosis.

Clinico-pathologic Conference

Acute Gastrointestinal Bleeding Complicated by Pleural and Pericardial Infection

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, P. N. (No. 230650), was a white female high school student, fifteen years of age, who was admitted to the Barnes Hospital on December 29, 1953, complaining of bloody diarrhea. The family history was non-contributory. The past history indicated that the patient had had the usual childhood diseases and frequent epistaxes during the early years of her life. She had never had other rheumatic manifestations, however. For most of her life she had been subject to recurrent attacks of asthma although the number of these seemed to be decreasing steadily. The only other pertinent fact in the history was that in the year prior to the patient's admission to the hospital there was an epidemic of viral hepatitis in the town in which she lived.

The patient had been in good health until approximately fourteen days prior to admission when a slight sore throat developed coincident with the onset of her regular menstrual period. The menstrual flow, however, was abnormally heavy and was accompanied by severe lower abdominal pain. Twelve days prior to entry the patient noted anorexia, nausea and malaise but she did not have fever. Because of increasing malaise she remained home from school. Nine days before admission severe vomiting and diarrhea began. The patient was seen by a physician who gave her an injection of penicillin; he also prescribed a sulfonamide and a pink liquid, reported to contain bismuth subcarbonate and paregoric, to be taken orally. Despite these measures the patient continued to vomit large quantities of green fluid containing flecks of blood and her diarrhea persisted. The sulfonamide was discontinued without change in the symptoms. Eight days before admission to the Barnes Hospital the patient was hospitalized

elsewhere and was given fluids intravenously. Five days prior to entry she began to pass bloody stools and two days later complained of pain and tenderness in the right upper abdominal quadrant. She was given two blood transfusions, the second of which was discontinued because of a mild urticarial reaction. On the day before entry to the Barnes Hospital proctoscopic examination was reported as showing "a badly ulcerated bowel." The bloody diarrhea continued and just prior to transfer to the Barnes Hospital the patient was given another unit of whole blood.

At the time of examination in the emergency room the patient's temperature was 39.4°C., pulse 130, respirations 20 and blood pressure 110/50. She was a well developed, thin, tall white girl who appeared acutely ill. She was sweating profusely and was mildly confused. Her skin was cold and clammy. There was no lymph node enlargement. A small hemorrhage was noted in the right conjunctival sac. The fundi appeared normal. Examination of the ears, nose and mouth and pharynx was within normal limits as was examination of the heart and lungs. The abdomen was held taut and there was diffuse tenderness without spasm. No masses could be felt. The bowel sounds were markedly decreased. Rectal examination revealed a shaggy rectal mucosa; the gloved finger was covered with blood. There were no deformities of the bones and joints. The pulse was feeble and the extremities cold. The reflexes were physiologic.

The laboratory data were as follows: red blood cells, 6,000,000; hemoglobin, 17 gm. per cent; white blood cells, 35,900; differential count: 14 per cent band forms, 75 per cent segmented neutrophils, 7 per cent lymphocytes, 4 per cent monocytes. Urine; specific gravity, 1.020;

albumin, 4+; sugar, negative; centrifuged sediment, occasional white blood cell and one to two granular casts per high-power field; guaiac, negative; urobilinogen, negative; culture, *Pseudomonas aeruginosa*; examination for heavy metals, negative. Stool: grossly bloody; microscopic, negative for ova and parasites; culture, *Ps. aeruginosa*. Blood chemistry: non-protein nitrogen, 35 mg. per cent; sugar, 169 mg. per cent (glucose running intravenously); carbon dioxide combining power, 22.6 mEq./L.; sodium, 137.9 mEq./L.; potassium, 2.9 mEq./L.; chloride, 98 mEq./L.; cholesterol, 101 mg. per cent; total protein, 4.6 gm. per cent; albumin, 2.6 gm. per cent; globulin, 2.0 gm. per cent; cephalin-cholesterol flocculation test, 3+; thymol turbidity test, 1 unit; alkaline phosphatase, 5 Bodansky units. Typhoid and paratyphoid agglutination tests: negative. Blood culture: negative.

Immediately after completion of the physical examination the patient was transported to her hospital room. On arrival there her blood pressure was unobtainable. An hematocrit drawn at this time was 60 per cent. Emergency therapy for shock was instituted, and in the next three hours the patient received 2,000 cc. of whole blood. Her systolic blood pressure rose to 100 mm. of mercury. During this period she vomited dark red blood and became cyanotic. Oxygen was administered and the cyanosis cleared. Seven hours after admission, when the patient's condition was stabilized, a limited proctoscopic examination was performed. The mucosa was noted to be granular, very friable and actively bleeding. Shortly thereafter the patient's temperature rose to 40°C., the pulse to 140 and the systolic blood pressure fell to 70. She was given fluids containing nor-epinephrine intravenously and also received two more units of whole blood. Vitamin K was administered intravenously. Salicylates by mouth and alcohol sponging were employed in an attempt to reduce the patient's temperature.

Ten hours after admission the prothrombin time was 39 per cent of normal. Blood indices were as follows: mean corpuscular volume, 92 cu. μ ; mean corpuscular hemoglobin, 28 $\gamma\gamma$; mean corpuscular hemoglobin concentration, 31 per cent; platelet count, 46,000.

The patient's condition again stabilized and she became more cheerful and alert. Her abdomen remained distended and exquisitely tender and bowel sounds were not audible.

Medication included propantheline bromide (pro-banthine®) and magnesium trisilicate and aluminum hydroxide (gelusil®) orally, penicillin and streptomycin intramuscularly and corticotropin intravenously.

Late in the first hospital day a paracentesis was attempted but no fluid was obtained. During the first twenty hours of hospitalization the patient's urinary output was only 550 cc. Approximately thirty hours after admission bleeding had stopped although ileus persisted. A bone marrow examination was performed and showed a cellular marrow which was normal except for the presence of young megakaryocytes. There was no evidence of active platelet formation. During the second hospital day the serum electrolytes were found to be within normal limits but the cholesterol had fallen to 44 mg. per cent, and the prothrombin time to 30 per cent of normal despite the administration parenterally of vitamin K. On the third hospital day rectal bleeding recurred; by this time the patient was able to take fluids and a diet by mouth and her urinary output had returned to normal. Antibiotic and corticotropin therapy were continued and vitamin K₁ oxide was also given. Because of the bleeding additional transfusions were necessary. On the fifth hospital day bromsulfalein retention was found to be 30 per cent at forty-five minutes.

The patient's temperature ranged between 37.2 and 38°C. On the seventh hospital day sigmoidoscopy was performed and acute ulceration of the rectosigmoid was demonstrated. On the ninth hospital day the presence of abdominal fluid became evident. Repeat laboratory studies at this time were as follows: urinalysis: specific gravity, 1.016; protein, negative; sugar, negative; sediment, 7 to 10 red blood cells per high-power field (non-catheterized specimen, patient menstruating). Non-protein nitrogen and serum electrolyte values: within normal limits; prothrombin time, 28 per cent of normal; total protein, 5.7 gm. per cent; albumin, 2.9 gm. per cent; globulin, 2.8 gm. per cent; cephalin-cholesterol flocculation test, \pm ; thymol turbidity test, 3.4 units; alkaline phosphatase, 4.2 Bodansky units; cholesterol, 44 mg. per cent; total bilirubin, 1.62 mg. per cent; sodium bilirubinate, 0.34 mg. per cent; bilirubinogen, 1.28 mg. per cent.

On the eleventh hospital day the platelet count was 300,000 per cu. mm. The patient continued to pass bloody stools and required

frequent transfusions. Abdominal distention was unaffected by all therapeutic measures. On the fourteenth day an "obstruction series" was obtained and showed obstruction in the region of the distal transverse colon.

The following day the patient began to bleed from the rectum more profusely, and passed a large number of bloody stools. She complained of epigastric and right upper quadrant pain. Transfusions were continued. Her temperature rose to 39°C. and remained elevated for the next three days. On the fifteenth hospital day penicillin and streptomycin were discontinued and tetracycline was given in a dosage of 250 mg. every six hours. A barium enema was performed and showed ulcerative sigmoiditis. Repeat proctoscopic examination showed no changes from those reported earlier. Marked tachycardia developed, the pulse rate rising to 156. There was no response to carotid sinus pressure or to the Valsalva maneuver. Digitalization was carried out and the patient's rate slowed to 130 per minute. Physical examination revealed dullness to percussion and distant breath sounds at both bases. Cardiac enlargement was noted. The heart sounds were distant and there was a faint cardiac impulse. Chest films taken at this time were interpreted as showing bilateral pleural effusion, cardiac enlargement and ? pericardial effusion. An electrocardiogram showed only low voltage.

On the twentieth hospital day a left thoracentesis was performed and 600 cc. of straw-colored fluid were obtained. The fluid had a specific gravity of 1.010, and contained 4,000 cells with acid, 75 per cent of which were segmented neutrophils. The protein was 1.3 gm. per cent. Gram and acid-fast stains showed no organisms. Cultures of the fluid were negative for pyogenic and acid-fast bacteria. On the following day pericardiocentesis was performed and 300 cc. of brownish red fluid were removed. The pulse rate dropped from 145 to 108 immediately after the procedure was completed but soon returned to 140. Specific gravity of the pericardial fluid was 1.010. It contained 28,000 cells without acid and 12,000 with acid, 80 per cent of which were segmented neutrophils. No organisms could be seen on smear and a cell block was reported as "no diagnosis made." On the same day an abdominal paracentesis was performed and 5,000 cc. of straw-colored fluid were obtained. The fluid had a specific gravity of 1.008. A smear was negative for bacteria and cultures were likewise negative.

In order to implement the patient's nutrition, tube feedings were begun. Despite this measure she continued to lose ground. A repeat electrocardiogram showed low voltage compatible with pericardial effusion. The patient's temperature ranged between 36.8 and 38.8°C. with daily spikes. In the last few days of life palmar erythema developed, and subsequently a diffuse erythematous macular rash appeared over her body. The heart sounds became progressively distant and tachycardia persisted. Examination of the chest revealed findings consistent with bilateral pleural effusions. A loud friction rub was heard over the right side of the chest and there was marked subcutaneous emphysema at the site of the previous paracentesis. Another thoracentesis was performed and 450 cc. of serosanguineous fluid were removed. The fluid contained 15,000 cells with acid of which 80 per cent were polymorphonuclear leukocytes. Specific gravity was 1.009. Cultures of pericardial fluid and of fluid from the right pleural cavity, obtained two days prior to patient's death, were reported positive for a coagulase-negative *Staphylococcus aureus* which did not ferment mannitol. Because of the recovery of this organism, erythromycin was begun in a dose of 200 mg. four times a day. On the day prior to death her serum electrolytes were within normal limits, cholesterol 74 mg. per cent and the prothrombin time 30 per cent of normal. The white cell count was 16,850, hemoglobin 13.9 gm. per cent and the differential showed a left shift. Urine was negative except for a trace of albumin and a few fine granular casts in the sediment. Another pericardiocentesis was performed and 225 cc. of bloody fluid were removed; the fluid had a specific gravity of 1.015, and culture confirmed the presence of *Staph. aureus*. Shortly after the procedure was completed the patient became cyanotic, extremely restless and thrashed about. Her blood pressure became unobtainable and despite various supportive measures she expired on January 21, 1954.

CLINICAL DISCUSSION

DR. VIRGIL SCOTT: Whatever the nature of the disease which we are to discuss today I sincerely hope that I shall not have occasion to see it again. The rapidity with which this process caused the death of this young girl is frightening to contemplate. As nearly as could be determined she had been well except for attacks of asthma

which were decreasing in frequency. The onset of her illness was heralded by a sore throat and abdominal cramps; the latter were thought initially to be associated with a normal menstrual period. Subsequently symptoms of a fulminating constitutional illness developed with bloody

general discussion, Dr. Elliott, will you discuss the films?

DR. GLADDEN V. ELLIOTT: Since the patient's major problem presumably centered about an intra-abdominal disease it will perhaps be best to review the gastrointestinal films first. As noted

TABLE I
RESULTS OF SELECTED LABORATORY EXAMINATIONS

Hospital Day	Units of Blood	Red Blood Count (millions)	Hemoglobin (gm. %)	White Blood Count	Platelets	Prothrombin Time (% normal)	Cholesterol (mg. %)	Albumin (gm. %)	Globulin (gm. %)
1	4	6.0	17.0	35,900	46,000	30	101
2	1	5.6	17.8	16,350	88,000	22	...	2.6	2.0
3	4	30	44
4	15.6	12,200
7	..	5.2	15.0	19,700	824,000	35	...	3.2	2.2
11	300,000	..	104
14	6	6,000	215,000	48	...	2.7	2.7
15	4
19	1	4.1	...	12,000	186,000
23	..	4.6	13.9	16,850	50,000	35	74	2.0	2.9

diarrhea which persisted until her death. Actually, during most of the short course she did not have true diarrhea but rather passed almost pure blood. The protocol relates in detail the course of the illness—a large number of studies was performed but despite these studies and the intensive therapy, the outcome was unaltered. There are several points to be emphasized. The persistent passage of blood per rectum has already been mentioned; it should be remembered that although the patient vomited blood on her first day in the Barnes Hospital, hematemesis did not occur. There were three distinct febrile episodes during her hospital course, the first two associated with bleeding and the last with both bleeding and infection. Between these episodes the temperature varied between 37.2 and 38°C. The patient's course was marked by frequent bouts of abdominal pain; and abdominal distention was a prominent feature throughout. Ascites became evident on the eighth hospital day.

Some of the pertinent laboratory data are given in Table I. The bacteriologic studies were of interest in that *Ps. aeruginosa* was recovered from both the urine and stool and a strain of *Staph. aureus* from pericardial fluid. Isolation of the latter organism occurred late in the illness—two days before death. Before we begin the

in the protocol, the first radiologic examination was an obstruction series on the fourteenth hospital day. This form of examination is a modification of the so-called scout film and includes films with the patient erect, and in the lateral position so as to include the rectal area. The purpose of the technic is to enable the radiologist to detect air-fluid levels and the distribution of gas. In this case the films demonstrated moderate distention of the ascending colon, the transverse colon and, to a lesser degree, of the stomach. These findings, coupled with the virtual collapse of the descending colon and rectum and slight distention of the proximal area, were interpreted as indicating obstruction in the distal transverse colon. However, in view of the history and because the patient had ascites when the films were made, this interpretation should be accepted with some reservation. Three days later the patient had a barium enema. It was with considerable hesitancy that this examination was performed; not only was the patient's general condition precarious but there was also the hazard of perforation. The contrast medium was administered with the utmost caution. The patient was able to retain it only to the splenic flexure, and no attempt was made to get barium beyond that point. Once again the films revealed moderate distention of the transverse

colon and lack of distention of the descending colon. On several of the films there was marginal serration which, taken with the history and proctoscopic observations, led us to make a diagnosis of ulcerative sigmoiditis. It should be noted, however, that the radiologic findings were surprisingly minimal when considered in the light of the clinical course.

The only other films obtained were of the chest; two and a half weeks after admission the findings included bilateral pleural effusions, and a large globular cardiac shadow consistent with pericardial effusion. A second chest film, obtained two days prior to death, showed further increase in the amount of pleural fluid and in the cardiac size.

DR. SCOTT: Dr. Wood has asked for additional comment on the electrocardiographic findings. During the patient's hospital stay three electrocardiograms were made. The first one on the eighth day showed sinus tachycardia with a rate of 100 per minute, and an abnormal form of ventricular complex. Twelve days later, on the twentieth hospital day, there was a sinus mechanism with a rate of 120. The voltage was lower than it had been earlier. Low voltage, also described on the twenty-third hospital day, was more marked in the precordial leads and was interpreted as being compatible with a pericardial effusion. At the outset of the discussion I would like to invite members of the staff to suggest diagnostic possibilities which we shall list and subsequently discuss in more detail. Dr. Glaser, would you begin?

DR. ROBERT J. GLASER: One possibility, of course, is fulminating acute ulcerative colitis—this case is as acute and fulminating as any of which I have ever been aware.

DR. LILLIAN RECANT: Fulminating viral hepatitis should likewise be considered.

DR. SCOTT: The protocol states that there was an epidemic of infectious hepatitis in the town in which the patient lived about a year before. Dr. Lonergan, can you contribute any additional information on this point.

DR. WARREN M. LONERGAN: Although the patient probably was exposed to infection, there was no evidence in the history that she had had hepatitis.

DR. EDWARD MASSIE: I would like to suggest tuberculosis involving the gastrointestinal tract. If indeed she had tuberculosis, it probably involved other organs as well.

DR. W. BARRY WOOD, JR.: Acute bacterial

enteritis due either to *Ps. aeruginosa* or to staphylococcus could have been the primary disease.

DR. SCOTT: Should infection due to the dysentery bacillus be included?

DR. WOOD: Yes, it should but I believe that one of the other two organisms was more likely.

DR. HAROLD SCHEFF: My thoughts were similar to Dr. Wood's in regard to bacterial enterocolitis; in addition, mention should be made of two other infections, amebiasis and histoplasmosis.

DR. RECANT: May we also include collagen disease, Dr. Scott?

DR. SCOTT: Which one did you have in mind?

DR. RECANT: I'm afraid I can't be more specific, but diffuse vascular disease can produce bizarre clinical patterns.

DR. SCOTT: This patient exhibited a number of hematologic abnormalities during her illness. Is there a primary hematologic disorder which should be included in the differential diagnosis, Dr. Loeb?

DR. VIRGIL LOEB, JR.: Not in my opinion.

DR. SCOTT: The patient didn't have thrombotic thrombocytopenia purpura, did she?

DR. LOEB: No.

DR. CARL V. MOORE: May I comment on the thrombocytopenia? This young girl had a disease which involved multiple organ systems, and acute bacterial infection, disseminated tuberculosis or collagen disease could have been responsible. Secondary thrombocytopenia is not uncommon in any one of the three, so that it could be explained on this basis. One should also include disseminated histoplasmosis although it seems less likely.

DR. SCOTT: What about secondary thrombocytopenia in ulcerative colitis or infectious hepatitis?

DR. MOORE: If it occurs in either one, it must be rare.

DR. SCOTT: I was able to find in the literature three cases of hepatitis with which there was associated thrombocytopenia, one of them described in 1943 by Woodward at the University Hospital in Baltimore. Whether the thrombocytopenia was coincidental or related to the underlying disease, I can't say. Does anyone else have information about the occurrence of thrombocytopenia in ulcerative colitis?

DR. ALBERT I. MENDELOFF: In the more characteristic forms of ulcerative colitis anemia is common but thrombocytopenia is certainly

unusual. If this patient had ulcerative colitis, it was a most unusual example of the disease; and in view of its acute nature, one would not be too surprised even by the occurrence of thrombocytopenia.

DR. AMOZ CHERNOFF: I was interested by the fact that the thrombocytopenia seemed to follow a rather cyclic course. At least there was one occasion when the platelet count returned to within normal limits despite the fact that the patient's primary disease process had not improved.

DR. SCOTT: Actually, I believe she was better at the time her platelet count was within normal limits. That was during the second week and in this period she stopped bleeding and her temperature came down to relatively normal levels. I think, therefore, that there may have been some correlation between the clinical improvement and the return of the platelet count to normal.

DR. CHERNOFF: Is it possible that the platelet depression was related to the transfusions? I looked at the hospital record and it was my impression that thrombocytopenia seemed to occur at those times when the patient was receiving the most transfusions, a phenomenon which, if true, suggests that platelet reduction was due to an antigen-antibody mechanism.

DR. SCOTT: Your point is an interesting one. It should be mentioned in this regard that the transfusions were, for the most part, not accompanied by manifestations of transfusion reaction.

DR. CARL V. MOORE: Another possible explanation for the thrombocytopenia, Dr. Scott, is that the favorable platelet response initially represented an effect of corticotropin therapy.

DR. SCOTT: Are there other diagnoses which should be considered?

DR. MASSIE: I would like to suggest two others, namely, carcinoma of the gastrointestinal tract with widespread metastases or lymphoma.

DR. HENRY A. SCHROEDER: It seems to me in an acute illness such as this, with vomiting and enteritis one should consider certain forms of poisoning. Certainly mercury can produce vomiting, albuminuria and colitis. Was an attempt made to find out whether this girl might have ingested poison?

DR. SCOTT: There was nothing in the history to suggest that she had. She apparently had been in good health and in good spirits prior to the onset of the present illness. The urine was examined for arsenic after she came to this hospital and was negative.

DR. SCHROEDER: Even if she had taken a toxic substance, by the time she was admitted here it probably would have been excreted.

DR. SCOTT: Let us now turn to more detailed discussion of the individual entities which have been listed. Concerning viral hepatitis which you suggested, Dr. Recant, perhaps it would be helpful if we asked Dr. Shank to comment on the liver function studies.

DR. ROBERT E. SHANK: The results of the various hepatic function tests suggest some degree of dysfunction. We have seen an acute clinical course characterize subacute hepatic necrosis secondary to viral hepatitis, in some instances without jaundice. In this patient, there was no significant increase in serum bilirubin. Similarly, in severe, rapidly fatal cases the flocculation tests have not been remarkable, especially in the first days of the illness. In this patient the thymol turbidity remained within normal limits throughout and only one cephalin-cholesterol flocculation test was recorded as 3+. There was reduction in albumin which is recorded as between 2.0 and 3.2 gm. per cent. This value is distinctly low, and despite the fact that the patient was bleeding and consequently was losing considerable protein the blood was being replaced at a rapid rate and therefore the relatively low albumin content of the serum may have been indicative of some degree of hepatic failure. The lack of elevation of alkaline phosphatase is in keeping with the essentially normal bilirubin values and is another finding rather common in anicteric viral hepatitis.

DR. SCOTT: In that regard what was the significance of the patient's failure to respond to parenteral vitamin K therapy?

DR. SHANK: It is presumptive evidence of serious hepatic dysfunction, as is likewise the very low cholesterol value. We have seen very few cases in which the cholesterol has fallen to levels as low as it did here—44 mg. per cent, although it does happen occasionally in very severe thyrotoxicosis. The bromsulfalein retention of 30 per cent at forty-five minutes could have resulted either from hepatocellular damage or from disturbance in hepatic blood flow. In essence, although there is real evidence of hepatic dysfunction, I don't think it is possible to attribute it unequivocally to viral hepatitis. As a matter of fact, in my opinion it probably was not.

DR. SCOTT: Dr. Recant, Dr. Shank has suggested that although some measure of hepatic impairment was no doubt present his feeling is

that it did not arise as a result of viral hepatitis. Do you still wish to support the diagnosis?

DR. RECANT: I suggested the diagnosis as one which should be mentioned in passing but it does not necessarily represent the most likely possibility. There was one point which was of particular interest to me, and that was the normal thymol turbidity test which could have been due to a very low serum lipid value. That test depends on the presence of a lipo-protein complex, and thus may be normal if such a circumstance obtains, even in the presence of severe liver disease.

DR. SCOTT: Dr. Glaser, do you want to discuss ulcerative colitis as a diagnostic possibility?

DR. GLASER: Dr. Mendeloff's earlier remarks are pertinent, namely, that if this indeed was ulcerative colitis it was a form far different from that seen rather commonly. The etiology of ulcerative colitis is unknown anyway and on occasion a similar clinical picture may be produced by bacterial infection. Dr. Wood has already suggested the possibility of acute bacterial enteritis, and in this instance it would be difficult to rule out bacterial etiology. On the other hand, there certainly are cases, fortunately rare, which develop suddenly in patients who have enjoyed good health, and which appear to be ulcerative colitis of the less acute type but which run an alarmingly rapid course and terminate fatally in a period of weeks. I know of at least one other case which developed very suddenly in a healthy, young man and caused death in a period of days. Pathologic examination in that instance showed changes which were considered to be those of acute, non-specific ulcerative colitis. Therefore, I think that the latter diagnosis remains a very likely one but I know of no way to substantiate it short of pathologic examination.

DR. SCOTT: What about the hematemesis and the evidence of hepatic involvement? Are those compatible with ulcerative colitis?

DR. GLASER: The hematemesis was a rather transient phenomena wasn't it?

DR. SCOTT: Yes, it occurred only during the patient's first hospital day.

DR. GLASER: I would have to assume that the hematemesis was an incidental finding. As far as the liver dysfunction it seems to me that a disease as acute as this one was, involving as it did a great deal of bleeding, might well be expected to produce secondary changes in the liver.

DR. SCHEFF: It is known that patients with very acute ulcerative colitis may have ulcers in the mouth, lower esophagus and esophagus and stomach. These ulcers are superficial but can bleed rather massively. Also, as Dr. Glaser has suggested, patients with severe ulcerative colitis do show evidence of impairment of liver function.

DR. SCOTT: Dr. Massie, how likely is it that the patient had tuberculosis?

DR. MASSIE: She had fever, pleural and pericardial involvement and severe disease of the gastrointestinal tract, and tuberculosis can involve all of these structures; against the diagnosis, however, is the fact that the patient was apparently well until the sudden onset of the illness.

DR. SCOTT: You don't consider it the most probable diagnosis?

DR. MASSIE: No.

DR. RECANT: I think viral hepatitis ought to be looked on in the same way, that is, as a possibility but not the most likely one.

DR. SCOTT: Dr. Wood, do you want to enlarge on bacterial enteritis as the cause of this patient's demise?

DR. WOOD: Some of the reasons for my having suggested acute bacterial enteritis are as follows: this young woman suffered from an acute illness of sudden onset, characterized first by abdominal pain, a symptom which immediately suggests gastrointestinal involvement. Further, she had fever and a high leukocyte count with a left shift in the differential count, changes consistent with acute bacterial infection. Taken together, these factors seem to me to support acute bacterial enteritis as a very real possibility. Before continuing I would like to ask several questions. Was the stool specimen examined specifically for cells?

DR. SCOTT: The stool was examined microscopically and many red blood cells and white blood cells were seen. Neither ova nor parasites were present.

DR. WOOD: One would expect to find white cells in the stool in acute bacterial enteritis. The absence of ova or parasites helps to rule out amebiasis. May I also inquire about the method by which the stool was cultured? It is recorded in the protocol that *Ps. aeruginosa* was recovered from the stool. Was that the only organism recovered? Were cultures made on media which would have supported the growth of the staphylococcus?

DR. SCOTT: Stool specimens were obtained at the time of proctoscopy by means of a swab. In addition to the usual media for enteric pathogen, a blood agar plate was also inoculated so that had they been present staphylococci should have been recovered. Only pyocyaneus was isolated.

DR. WOOD: The presence of pyocyaneus is extremely significant because it is not usually present in the stool. The absence of staphylococci rules out fairly well staphylococcal enteritis which would otherwise have had to be considered. I have one final question. Was the blood culture negative?

DR. SCOTT: Yes, it was. However, there was only one culture taken and that early in the period of hospitalization.

DR. WOOD: Certainly if one supports the diagnosis of bacterial enteritis he has to assume that terminally there was bacteremia with involvement of myocardium in the form of abscesses leading to congestive heart failure. Since blood cultures were not obtained in the last few days of the patient's life this hypothesis cannot be refuted. One can, on the other hand, make a case against *Ps. aeruginosa* infection. Although the organism can produce acute ulcerative lesions, particularly in the small intestine, and may occasionally cause death, significant bleeding from the bowel is extremely uncommon in pyocyaneus enteritis. Nonetheless, taking all the evidence into consideration, I favor acute enteritis due to pyocyaneous infection as the most likely diagnosis.

DR. SCOTT: How do you explain the recovery of staphylococci from the pleural fluid terminally? Do you think that this organism gained a foothold because of the corticotropin therapy?

DR. WOOD: The recovery of the staphylococcus on at least two occasions is, of course, significant. Most staphylococci are resistant to penicillin and become resistant rapidly to other antibiotics. This patient received a number of antibiotics and may have acquired a drug-fast strain of staphylococcus which led to the terminal complications. As I previously indicated, if staphylococcus had been recovered from the stool, the entire illness could have been explained on the basis of staphylococcal enteritis. Since it was not, one has to attribute the gastrointestinal disease to *Ps. aeruginosa*.

DR. SCOTT: Other forms of bacillary dysentery were suggested but I think they need not be discussed further since they would be unlikely.

DR. WOOD: One final comment in regard to

the problem of infection with pyocyaneus. It is often difficult to tell whether this organism is actually producing disease or whether it is merely being "carried." Thus it would have been of interest to determine if the patient's serum contained agglutinins against the organism. If so, one would have evidence that the organism was indeed invading tissue.

DR. GLASER: Dr. Wood, aren't you surprised that pyocyaneus was not recovered from the fluids which accumulated in the various serous cavities? The organism grows readily and had it been important, I would have expected it to have gotten into the blood stream and then into the fluids.

DR. WOOD: One has to assume that pyocyaneus remained localized in the intestine, and that only the staphylococcus was blood-borne.

DR. SCOTT: The remaining suggestions—amebiasis, histoplasmosis, collagen disease, cancer, lymphoma and poisoning—deserve mention but none can be substantiated on the basis of the information available. I would like, therefore, to turn our attention to consideration of the problem of the serous fluids. The first signs of bilateral pleural fluid developed on the patient's twentieth hospital day. Thoracentesis was performed and 600 cc. of straw-colored fluid were obtained; the fluid contained 4,000 cells of which 75 per cent were polymorphonuclear leukocytes and had a specific gravity of 1.010. A pericardial tap shortly thereafter produced 300 cc. of brownish red fluid which contained 12,000 cells, 80 per cent of them polymorphonuclear leukocytes. The specific gravity was 1.010. No organisms were seen and none was recovered from the cultures. Following removal of the pericardial fluid the pulse rate fell transiently but soon returned to its previous level. Ascitic fluid obtained shortly thereafter had the characteristics of a transudate. Subsequently, as indicated already, *Staph. aureus*, coagulase-negative and non-mannitol fermenting, was recovered from both pleural and pericardial fluids. Dr. Wood, the high cell counts and low specific gravity readings are somewhat paradoxical, are they not?

DR. WOOD: I believe they can be explained if one assumes that the large number of inflammatory cells constituted a response to the infection whereas the large amount of fluid which accumulated was due to congestive failure arising on the basis of cardiac failure secondary to myocardial abscesses.

DR. SCOTT: Several additional points should be mentioned. According to the state health officer in charge of communicable diseases, in the first six months of 1953 five cases of viral hepatitis, most of which occurred in January and February, were reported from the town in which this patient lived. I was led to believe, however, that when there are five cases reported, many more may be presumed to have been present since disease reporting by physicians here, as in many other communities, leaves much to be desired. As far as hematemesis in viral hepatitis is concerned, ulcerative esophagitis has been described as has massive hemorrhage from the bowel on the basis of phlegmonous enteritis. With respect to the latter lesion, the cecum and ascending colon are the areas usually involved. Approximately 15 per cent of patients with fatal epidemic hepatitis present such changes. Further, 60 per cent of these cases have had ascites, and a fourth of this group also have had pleural effusions. However, Lucké's¹ report, from which these data were obtained, does not mention involvement of the rectum and sigmoid by phlegmonous enteritis. The most important evidence against viral hepatitis is the absence of jaundice in a patient who survived for as long as thirty-six days. The fatal cases of anicteric viral hepatitis that I was able to find succumbed within five days after onset of the disease.

Concerning ulcerative colitis there are case reports in which serum cholesterol values were below 100 mg. per cent. Also, as Dr. Scheff stated earlier, involvement of the upper gastrointestinal tract with vomiting and hematemesis are comparable with so-called fulminating acute ulcerative colitis. In addition, the prothrombin time may be decreased and may not respond to vitamin K. Dr. Moore, do you have anything to add?

DR. MOORE: Dr. Wood has made a convincing case for his suggestion of acute bacterial enteritis but the evidence that has been marshalled in favor of viral hepatitis is also impressive. I came to the conference with the view that disseminated tuberculosis was the most likely diagnosis and I still think so even though I realize that there are many arguments against this suggestion. On the other hand, tuberculosis can produce most of the changes that were recorded here except perhaps the very marked change in the rectal mucosa. I don't recall hav-

ing ever seen that in tuberculosis. What was the clinical diagnosis?

DR. SCOTT: Collagen disease.

DR. MOORE: And what is yours?

DR. SCOTT: I have never seen a disease such as this before. I suspect that it was infectious in origin, but unlike Dr. Wood, I don't think that it was bacterial. I suspect a viral etiology with involvement of the colon, perhaps of other portions of the gastrointestinal tract, and of the liver. Finally, there was evidence terminally of infection in the pericardium and right pleural cavity.

Clinical Diagnoses. ? Acute bacterial enteritis; ? fulminating acute ulcerative colitis; ? viral hepatitis; ? collagen disease; ? disseminated tuberculosis; staphylococcal pericarditis and pleuritis.

PATHOLOGIC DISCUSSION

DR. DAVID E. SMITH: The principal lesion in this case was in the colon, particularly in the cecum, ascending colon and transverse colon. The surface of the mucosa was eroded by numerous ulcers with ragged polypoid fragments of mucosa projecting between. Figure 1 illustrates the ulcers in the cecum, and the polypoid persistent mucosa is quite apparent. There was no exudate adherent to the surface of the ulcers which were arranged along the mucosa beneath the taenia. A lesser degree of the same type of change was present in the sigmoid colon and a few ulcers were present in the terminal ileum near the ileocecal valve. The colon contained a large amount of fresh and partially clotted blood, but the identification of a particular bleeding point was not possible. The peritoneal cavity contained 1,500 cc. of clear straw-colored fluid. Small recent thrombi were present in the mesenteric veins of the tributaries of the inferior mesenteric vein. These thrombi were irregularly distributed and none was apparent in the superior mesenteric veins that drained the region of the most prominent ulceration in the colon. The liver was of almost normal size but showed areas of wrinkling of the capsule and foci of subcapsular hemorrhage. On cut section the surface was a remarkably variegated pattern. (Fig. 2.) There were broad pale areas, other areas of a congested appearance and still others of a very intense reddish color with almost complete obliteration of the usual lobular markings. The latter were typical of so-called Zahn infarcts. Recent and organized thrombi were present in

¹ LUCKÉ, B. and MALLORY, T. B. The fulminant form of epidemic hepatitis. *Am. J. Path.*, 22: 867, 1946.

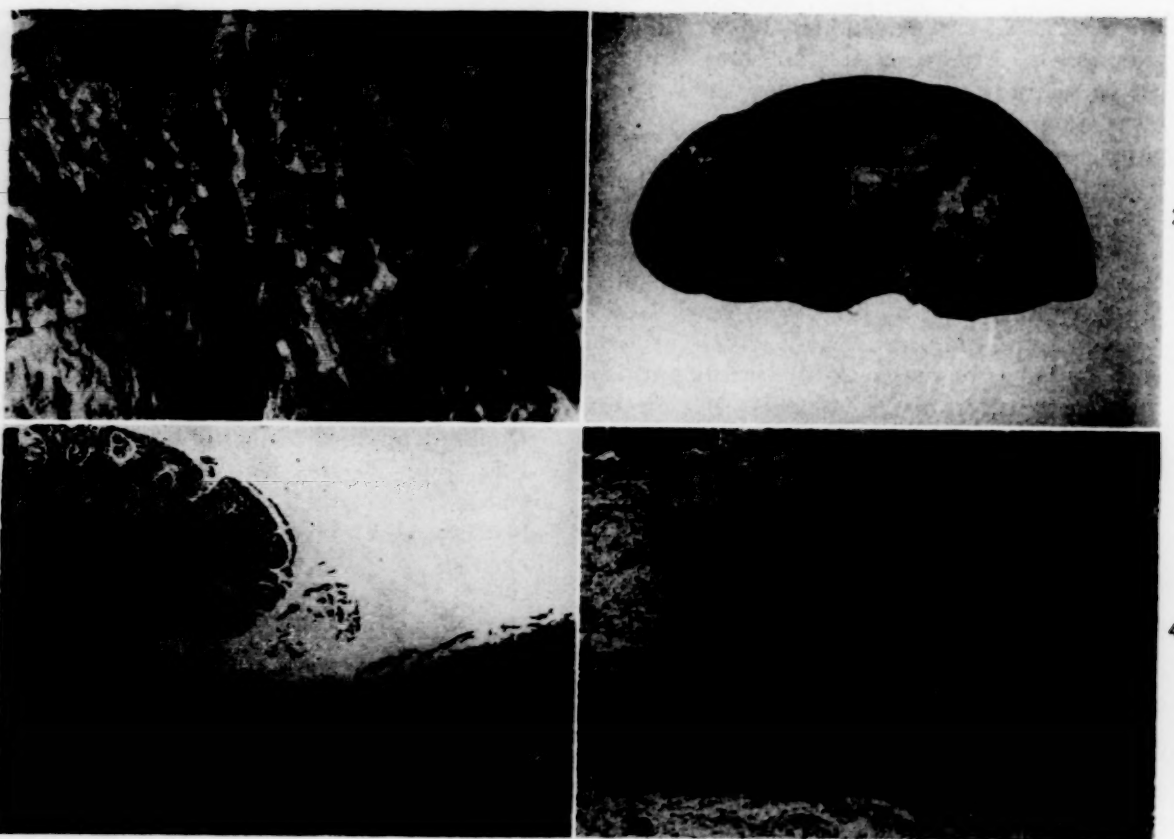


FIG. 1. Mucosa of the cecum showing clean-based ulcers and polypoid hyperplasia of the intervening persistent mucosa.

FIG. 2. The liver showing areas of congestion and Zahn infarcts with recent thrombi in the portal and hepatic veins.

FIG. 3. An ulcer in the colon with a clean base of granulation tissue immediately adjacent to the muscularis. No specific etiologic agent could be identified in these sections.

FIG. 4. Serosa of the colon showing a small organized thrombus partially occluding a vein. This thrombotic manifestation was widespread in the colon and other organs.

radicles of the portal vein and of the hepatic vein, and the portal vein was completely occluded for a distance of about 4 cm. in its course through the hilum of the liver.

The pericardial cavity contained 150 cc. of blood-tinged fibrinous exudate and there was a shaggy plastic serofibrinopurulent exudate over the surface of the heart. The heart was otherwise not remarkable. In the right pleural cavity there were 1,500 cc. of blood-tinged fluid and 700 cc. of similar fluid were present in the left pleural cavity. The pleural surfaces, particularly of the right lung, were covered by a fibrinous exudate. In all lobes of the lung there were small discrete abscesses 6 or 7 mm. in diameter surrounded by a thin zone of hemorrhage. Similar abscesses were identified grossly in the papillae of the kidneys, and *Staph. aureus* was recovered from these abscesses as well as from the heart's blood.

Sections of the ulcers in the colon, as is shown in Figure 3, show a mucosa with very prominent mucous cells in the walls of the glands. At the edge of the ulcer this mucosa overhangs the eroded area and the base of the ulcer consists of clean granulation tissue that lies directly on the muscularis. There is slight infiltration of inflammatory cells in the base and in the surrounding submucosa; however, there is no evidence of a particular or specific etiologic agent in these sections. The clean appearance of the ulcers is unlike that commonly seen in colitis due to *pseudomonas* in which cases there is usually a pseudomembrane formed over the areas of ulceration. This is apparently a relatively acute process which we can compare most closely to that of idiopathic ulcerative colitis.

Figure 4 is from the serosa of a portion of the colon and shows a small vein which is partially

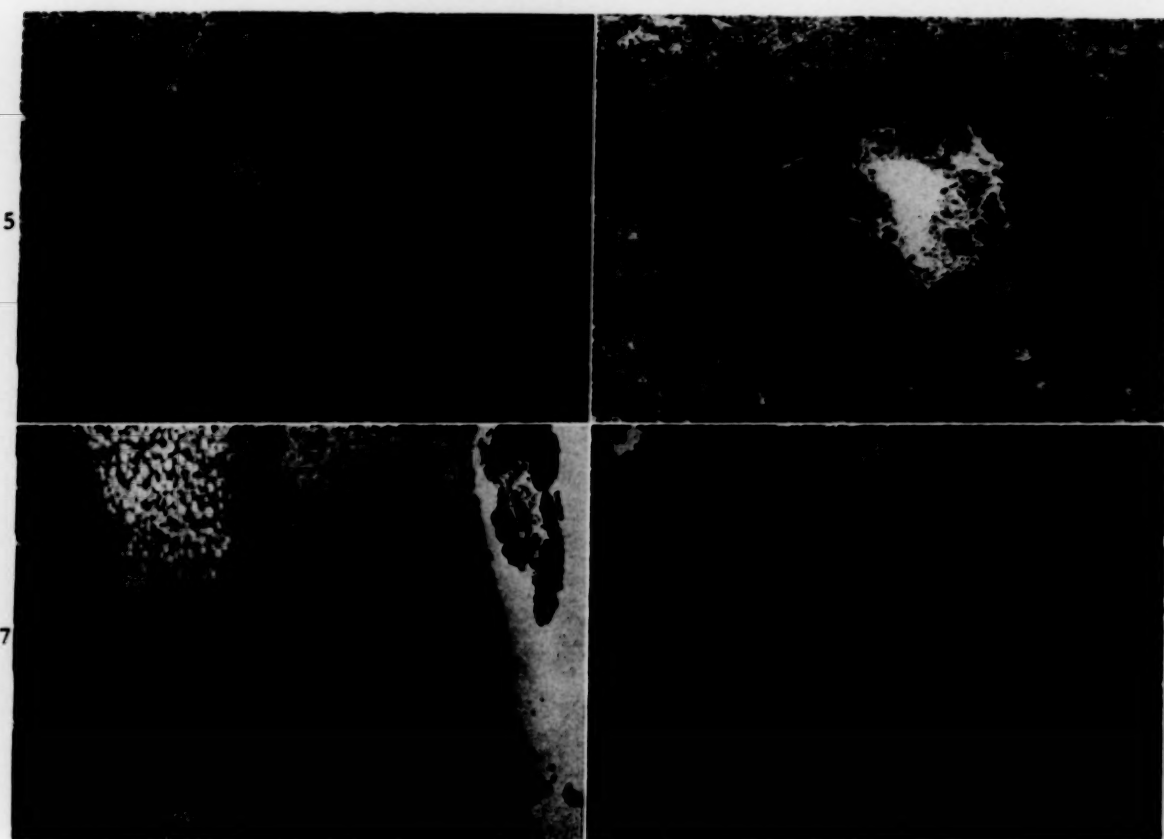


FIG. 5. The liver showing ischemic atrophy of hepatic cells and fibrosis, particularly around central veins. Similar areas of damage and scarring were present in portal areas as well as elsewhere in the liver.

FIG. 6. A relatively acute, small abscess in the lung. Similar abscesses were present in the kidneys and brain.

FIG. 7. Pericardium showing an organizing pericarditis. The state of reaction indicates a duration of a week or so.

FIG. 8. The kidney showing calcification in the distal tubules. This lesion has been described in cases of ulcerative colitis and as a sequela of lower nephron nephrosis.

occluded by an organized thrombus. Although such thrombi are numerous and widespread, it is remarkable that nearly all of them show a fairly complete degree of organization indicating a duration of the process that is definitely more than terminal and probably from two to five weeks of age. Similar small organized thrombi that do not completely occlude the lumens of the vessels in which they are located can be identified in the veins of the kidney, liver, spleen, mesentery and the pulmonary arteries. In addition, there are larger thrombi in the hepatic veins which also show some degree of organization. The widespread and organized condition of these thrombi suggest they are related to some event that occurred days or weeks before the patient's death and are due to an influence that operated in most of the tissues. It might be suggested that they arose during

periods of stagnation and concentration of the blood during the prominent episodes of shock in the early part of the clinical history, although such is certainly not a commonly recognized complication of shock. In the liver, as is shown in Figure 5, there are broad areas of relatively bland centrallobular necrosis, particularly in the areas adjacent to the veins that are occluded by thrombi. The picture is essentially one of ischemic atrophy and loss of hepatic cells without evidence of inflammation. This damage is extensive and involves not just the central areas but extends to portal areas in other sections.

One of the small abscesses present in sections of the lung is illustrated in Figure 6. These are of acute nature and have distinct, although not extensively organized walls. Similar abscesses were present in the kidney and a number of very small abscesses were encountered throughout the

cortex in sections of the brain. The pericardium (Figure 7) shows a thick organizing pericarditis. This amount of tissue reaction is indicative of a process of several days to a week in duration, and the lesion is further evidence of the widespread infectious manifestations that were present during the latter portion of the patient's illness.

The last illustration (Fig. 8) is from the kidney. In addition to the abscesses, the kidney contains small masses of calcification in the distal tubules. This phenomenon of calcification in the tubules of the kidneys has been noted in many reports of idiopathic colitis; however, similar lesions have also been ascribed to the effects of lower nephron nephrosis. In this particular case there was no recognized episode of nephrosis, although there were certainly several periods of severe shock. It is impossible to be certain whether these calcified casts of destroyed epithelium are those that accompany idiopathic colitis for no known reason or whether they indicate a small amount of lower nephron nephrosis at one time in the course of the disease.

In summary, this is a case of an acute ulcerative process involving particularly the right side of the colon in which no particular etiologic agent or process can be identified. We consequently have called it acute ulcerative colitis, recognizing the extreme variability, both clinically and pathologically, of features of that

syndrome. The lesion in the colon has been accompanied or followed by multiple thrombotic events involving particularly the portal system and resulting in severe atrophy of the liver with scarring and thrombosis. Thrombi are also present in many other organs suggesting the operation of a systemic factor which is essentially unidentified but might be related to the severe periods of shock in the patient's clinical history. As an additional and final event, there was, during the last week or days of life, the acquisition of a staphylococcal septicemia with localization of abscesses in the kidneys, lungs, brain, pericardium and pleura.

Final Anatomic Diagnoses. Acute ulcerative colitis involving the cecum, ascending colon, terminal ileum and sigmoid colon. Fluid and clotted blood in the colon. Recent and partially organized thrombi in subserosal veins of the colon, interhepatic tributaries of the hepatic vein and in the portal veins, splenic veins, inferior mesenteric veins, small veins in the kidney and small branches of the pulmonary arteries. Multiple abscesses in all lobes of the lungs, the kidneys and the brain. Organizing pericarditis and pleurisy.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

Research Society Abstracts

Western Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SEVENTH ANNUAL MEETING, PORTLAND, OREGON, JANUARY 29 AND 30, 1954

EFFECT OF DISODIUM CALCIUM VERSENATE ON IRON EXCRETION IN MAN. *William G. Figueroa, William S. Adams,* Samuel H. Bassett, Leon Rosove and Frances Davis.* V. A. Center, and Dept. Medicine, Univ. California Medical Center, Los Angeles, Calif.

The effect of oral and intravenous administration of disodium calcium versenate (EDTA) on iron excretion was studied in five patients. Two of these patients had primary hemochromatosis, one hypogonadism, one had a gastrectomy for leiomyosarcoma, one was normal. The patients with primary hemochromatosis and the one with hypogonadism were placed on iron balance during the study.

The intravenous administration of disodium calcium versenate was found to increase the twenty-four-hour urinary excretion of iron in the patients with primary hemochromatosis from four- to tenfold, depending on dosage. The twenty-four-hour urinary excretion of iron in one of these patients increased from 0.4 mg. to 5.6 mg. when 4 gm. of the drug were administered intravenously. No further increase in urinary output of iron was obtained when the dosage was increased to 8 gm. per day. The patient with hypogonadism also had moderate increase in urinary iron output. The normal subject and the patient with gastrectomy had only a very slight increase in urinary iron excretion, from 0.4 to 0.8 mg. per twenty-four hours. Oral administration of the drug in a dosage of from 5 to 8 gm. per day failed to increase the urinary output of iron. Preliminary data on the patients on balance suggest that oral administration of the drug in this dosage does not materially affect the fecal iron excretion.

No toxicity of the drug was noted, with the exception that one of the patients with hemochromatosis developed a slight diarrhea during the last day of study after he had received a total of 40 gm. of the drug intravenously during a

five-day period. No diminution of prothrombin activity was observed. The practicality of the use of this drug to detect abnormal amounts of iron in the body is being investigated.

EFFECT OF CORTISONE ON EXPERIMENTAL HEMOLYTIC ANEMIA. *Robert S. Evans* and Russell S. Weiser.* V. A. Hospital, and the Depts. Medicine and Microbiology, Univ. Washington School of Medicine, Seattle, Wash.

Cortisone administration diminishes the rate of blood destruction in patients with autoimmune hemolytic anemia. Study of experimental hemolytic anemia in rabbits was undertaken to gain further information on the action of cortisone on the *in vivo* destruction of red cells by antibodies. An antirabbit red cell serum was produced by injecting washed rabbit red cells into goats. The hyperimmune goat serum was injected intravenously into both cortisone-treated and control rabbits in doses of 0.5 ml., 0.75 ml. and 1.0 ml./kg. body weight. The average percentage drop in hematocrit and the rate of elimination of Cr⁵¹ tagged cells was less in the cortisone-treated animals than in the controls. A greater increase in hypotonic fragility of the red cells in the cortisone-treated group suggested a sparing of abnormal cells from destruction. Sensitization of red cells by goat globulin as demonstrated by the antiglobulin serum technic was equal in amount and duration in the two groups. A "bivalent" saline agglutinin present in the goat serum was not demonstrable *in vitro* after the first twenty-four hours but sensitization by a "univalent" goat serum antibody was detected by the antiglobulin serum method for five to seven days.

An unexpected finding was a fall in hematocrit averaging 18 per cent in the animals receiving the 20 mg. of cortisone daily prior to the administration of immune serum. The hematocrit drop was due to an increase in plasma volume as measured by Cr⁵¹ technic. The cortisone effect on plasma volume could be partially reduced by

* Asterisks indicate members.

salt restriction and starvation, and was not duplicated by daily injection of 3 mg. of desoxycorticosterone acetate. The changes in plasma volume which could not be controlled may have influenced the severity of the hemolytic anemia and accounted for the differences between the two groups.

However, cortisone administration did not interfere with sensitization of red cells or prevent destruction of sensitized cells to the degree that would account for the beneficial effect of the hormone in autoimmune hemolytic disease.

EXPERIMENTAL PRODUCTION OF RED CELL AUTOIMMUNIZATION. *Arno G. Motulsky and William H. Crosby (introduced by Clement A. Finch).* Dept. Hematology, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C., and Dept. Medicine, Univ. Washington, Seattle, Wash.

The antigenic stimulus for production of "autoantibodies" in human acquired hemolytic anemia remains obscure. Erythrocyte surface membrane changes have been postulated to explain the immunologic paradox of autoimmunization in such patients.

Experimental erythrocyte autosensitization was elicited in the following manner. Guinea pig red cells were emulsified with Freund's adjuvant mixture and injected subcutaneously at weekly intervals into the same animals from which they were obtained (series 1). The erythrocytes of other guinea pigs (series 2) were separately incubated with influenza virus. After elution of the virus and washing, the treated erythrocytes were emulsified with the adjuvant and injected in a similar manner. Evidence of autosensitization was sought by performing direct Coombs' tests on guinea pig red cells with a specially prepared anti-guinea-pig-serum rabbit-serum.

Definitely positive Coombs' tests could be demonstrated after six weeks in ten of eighteen animals of series 1. Essentially similar results were obtained in series 2; after seven weekly injections seven of fourteen animals showed positive Coombs' tests. The Coombs' test of a control series of eighteen guinea pigs injected only with Freud's adjuvant remained consistently negative for eight weeks.

Cessation of injections resulted in disappearance of positive Coombs' tests in most animals within a few weeks. Booster injections again produced positive Coombs' tests in some in-

stances. Hemolytic anemia could not be shown in any animals by conventional methods.

Saline cold agglutinins were found inconsistently in both Coombs' positive and Coombs' negative animals. However, persistence of positive direct Coombs' tests when all procedures were carried out at 37°C. ruled out cold agglutinins as the source of the positive Coombs' test. No other circulating antibodies (indirect Coombs' test, iso- and autoagglutinins and hemolysins using both saline and albumin as diluents) could be demonstrated in any of the Coombs' positive animals.

These results indicate that red cell autoimmunization as demonstrated by a positive Coombs' test can be experimentally produced.

MICROSPECTROPHOTOMETRIC ESTIMATION OF DESOXYRIBONUCLEIC ACID (DNA) CONTENT OF INDIVIDUAL PLASMA CELLS IN MULTIPLE MYELOMA AND NON-SPECIFIC PLASMOCYTOSES. *Nicholas L. Petrakis and Louis J. Folstad.* Laboratory of Experimental Oncology, Cancer Research Institute, and Dept. Medicine, Univ. California School of Medicine, San Francisco, Calif.

Myeloma cells have been generally considered to be neoplastic cells but differentiation from non-specific plasmacytoses may often be difficult on purely morphologic evidence. The present studies were undertaken to determine whether or not myeloma plasmacytoses differed from non-specific plasmacytoses with respect to their DNA content. The DNA of the nucleus has been shown to be immediately related to chromosome structure and mitotic activity, and to exhibit quantitative alterations in malignant cells. The microspectrophotometric technic employing the Feulgen reagent was used to determine the relative amount of DNA in the nuclei of individual myeloma and plasma cells aspirated from the bone marrow and of normal circulating lymphocytes.

Individual myeloma cells were found to contain markedly elevated amounts of DNA as compared to those found in non-myeloma plasma cells. The myeloma cells demonstrated a polyploid DNA series, i.e., to occur in geometric multiples (2:4:8) of the amount of DNA present in normal lymphocytes. The degree of DNA "ploidy" was directly related to the morphologic stage of immaturity. Polyploid DNA values were found in plasma cells from the non-specific plasmacytoses studied.

The findings suggest the presence of a basic

alteration in the quantitative DNA-chromosome relationship in myeloma cells, and offer further evidence in support of the separation of the myeloma plasmocytoses from other non-specific bone marrow plasmocytoses.

NUMBER AND DISTRIBUTION OF HUMAN HEMIC CELLS. *Edwin E. Osgood.* Dept. Medicine, Division of Experimental Medicine, Univ. Oregon Medical School, Portland, Ore.

Data now available from our own work and that of others on the duration of the different stages of differentiation of the hemic cells have made possible a calculation of the total number of these cells in the body. Since for non-dividing cells in the steady state the number in each stage of development will be proportional to the life span in that stage, the number of nucleated erythrocytes may be calculated from the ratio of their life span to the life span of the erythrocytes in the blood. The number of nucleated cells of the granulocytic series in the marrow may be calculated from the ratio of the exclusively marrow stages to the nucleated erythrocytes, and the number of segmented neutrophils from the ratio of these granulocytic series life spans. Such calculations show that there are at least 400 gm. of segmented neutrophils outside the marrow and only 10 gm. of these are present in the circulating blood. There is evidence also that most of the mature lymphocytes exist in the body outside the blood stream and hematopoietic organs. In other words, leukocytes are not primarily blood cells. The fact that only $\frac{1}{40}$ of the leukocytes outside the marrow are present in the blood explains the rapid disappearance of transfused leukocytes, the rapid appearance of leukocytes in pneumonic consolidations, abscesses, or in pleural and peritoneal cavities, and many other observations which otherwise seem difficult to account for.

ESSENTIALITY OF THE HEPATIC RETICULO-ENDOTHELIAL SYSTEM IN NORMAL CHOLESTEROL METABOLISM. *Meyer Friedman* and Sanford Byers.** Harold Brunn Inst., Mount Zion Hospital, San Francisco, Calif.

The role of the hepatic reticulo-endothelial system in cholesterol metabolism was investigated in various mammals by various histologic and physiologic technics.

A considerable part of cholesterol, when ingested by the rat, is taken up first by the Kupffer cells and then transferred to the hepatic paren-

chymal cells. Interference with this process effects four phenomena: (1) failure of deposition of dietary cholesterol in liver, (2) persistence of chylomicrons in blood, (3) hyperlipemia and (4) hypercholesteremia. Similar interference with the function of the Kupffer cell in the dog and rabbit leads to the same phenomena. Interference with the function of the Kupffer cell, however, in the starved animal does not interfere with the endogenous phases of synthesis and catabolism of cholesterol occurring therein.

These findings suggest that the hepatic reticulo-endothelial cells play an important and essential role in the mammals' ability to utilize dietary cholesterol and that with its failure, hyperlipemia and hypercholesteremia may occur. The implications of these observations will be discussed.

METABOLISM OF HEXOSES IN THE BODY. *Arne N. Wick* and Douglas R. Drury.** The Scripps Metabolic Clinic, La Jolla, and Univ. Southern California, Los Angeles, Calif.

The four common hexoses, glucose, fructose, galactose and mannose, are handled by the extrahepatic tissues in various ways which in some cases are influenced by insulin. Glucose, galactose and mannose can enter the extrahepatic cells at a slow rate, which can be markedly accelerated by insulin. Two of these hexoses, glucose and mannose, can be oxidized by the intracellular enzyme system and the rate of oxidation is increased by insulin. The intracellular enzyme system has little if any capacity to oxidize galactose although its intracellular transfer is accelerated by insulin. Fructose does not enter the extrahepatic cells to any measurable degree and this is not changed by insulin. Consequently, this hexose is not oxidized by the extrahepatic cells. Other hexoses and related compounds react like fructose.

The treatment of hexoses by the liver is altogether different. All of the common hexoses and related compounds seem to be able to enter the liver cells even without the mediation of insulin. Here fructose can be oxidized as well as mannose. Preliminary work indicates that other hexoses will enter and may be used by the liver cells even in the diabetic animal.

LIMITATIONS OF AEROBIC METABOLISM IN THE NEWBORN. *Ruth T. Gross.* Dept. Pediatrics, Stanford Univ. School of Medicine, San Francisco, Calif.

The energy released in the metabolism of glucose is derived primarily from the aerobic phase, the Krebs' cycle. It has been assumed, however, that in early postnatal life there is a period of transition during which reliance on oxidative mechanisms is not complete. In this study the technic of arterial and venous sampling of both glucose and citric acid, a component of the Krebs' cycle, has been utilized to make dynamic observations of the ability of the newborn infant to metabolize carbohydrate at an oxidative level.

Observations have been made on thirty-six infants and children ranging from the day of birth through three and one-half years, in both the fasting and postprandial states. In infants beyond the first week of life there occurred a venous level of citric acid exceeding the arterial level in response to fasting. This piling up of citric acid in the venous blood would seem to indicate that as glucose becomes less readily available there is a partial block in the operation of the Krebs' cycle beyond the formation of citric acid. In infants less than one week of age the "block" was found to occur even in the postprandial state. These data substantiate the hypothesis that oxidative mechanisms have not yet been well established in the immediate postnatal period.

The validity of this type of assessment of carbohydrate metabolism has been further tested in older children with certain carbohydrate disorders: galactosemia, diabetes and dwarfism.

STUDIES IN HUMAN PLASMA PROTEIN FORMATION, COMPARATIVE FATES OF I^{131} LABELED ALBUMIN, AND ENDOGENOUSLY SYNTHESIZED PLASMA PROTEIN FROM S^{35} LABELED AMINO ACID PRECURSORS. *Sheldon Margen,* Harold Tarver and Judith Lange.* Dept. of Physiol. Chem., Univ. California Medical School, San Francisco, Calif.

As part of the long range studies of the dynamic fate of plasma proteins the following studies have been carried out in a group of twenty normal males. Two labeled compounds have been administered simultaneously: (1) I^{131} tagged albumin, to determine the turnover pattern of an exogenously labeled protein moiety and (2) S^{35} labeled cystine or methionine, to determine the incorporation and disappearance of the S^{35} labeled albumin and globulin fractions synthesized *in vivo* from the labeled amino acid precursors. From these experiments

the following results have been obtained: (1) The I^{131} albumin disappearance curve may be resolved into three components which probably represent (a) intravascular-extracellular equilibrium, (b) extracellular-intracellular equilibrium, (c) metabolic degradation of the iodinated albumin. (2) The half-life of the metabolic portions of the albumin curve is 10 ± 0.5 days. (3) Denatured albumin is very rapidly removed from circulation. (4) In the experiments with S^{35} labeled amino acids there is no significant fall in albumin specific activity for the first twelve to fifteen days of the experiment after which a gradual non-exponential fall occurs.

On the basis of these results the following conclusions are drawn: (1) The S^{35} labeled amino acid technic is not valid for measuring albumin turnover in humans because of "re-entry" phenomenon from other S^{35} labeled precursors. (2) The I^{131} labeled technic may be valid but recent work has shown differences in electrophoretic behavior of I^{131} labeled from non-labeled albumin. The question of whether the iodine labeled material represents a "normal" biological protein is likewise unsettled. This latter problem is being currently investigated by comparing the fate of I^{131} labeled proteins vs. internally S^{35} biologically labeled proteins and will be discussed.

BIOSYNTHETIC DETERMINATION OF TURN-OVER RATES OF VARIOUS PLASMA PROTEINS IN NORMAL AND CIRRHOTIC MAN. *Wade Volwiler,* Patrick D. Goldsworthy, Marion P. MacMartin, Patricia Ann Wood, Gertrude Douglas and Iran R. Mackay.* Seattle, Wash.

The mechanisms responsible for alterations in various components of the plasma proteins in diseased states are largely unknown. An abnormal life-span of certain plasma protein molecules has been suggested as a partial cause of the markedly abnormal amounts of specific plasma components observed in various diseases.

Biosynthetic labeling of plasma proteins in normal and cirrhotic man has been accomplished with S^{35} tagged cystine. Turn-over rates of specific plasma proteins have been determined by two technics: (1) oral administration of labeled precursor with serial sampling of plasma or serum for measuring rate of isotope loss from proteins, and (2) transfusion of normal donor-labeled S^{35} plasma into recipients with subsequent serial sampling of plasma or serum to determine rate of isotope decline in protein

fractions. Fractionation of plasma and serum samples has been conducted as follows: albumin: Batchelor-Brown modification of Cohn 10 method; gamma globulin: Cohn 10 method; beta-1-lipoprotein: Cohn 10 method with subsequent ultracentrifugal flotation by the technic of

HALF-LIFE (DAYS) OF VARIOUS PLASMA PROTEINS
(S-35 cystine—12 experiments)

	Albu- min	Cohn I + III	Beta-1- lipo- protein	Fibrino- gen
Normal Subjects				
1	26.0	6.2
2	41.0	7.8
3	24.0	4.0	4.5
4	26.5	5.0	6.0
5*	16.0	4.0	4.0
6*	24.0	2.5	3.5
Advanced Portal Cirrhosis				
1	25.0	11.0
2	22.0	9.0
3	16.0	10.5
4	7.7	11.0
5*	24.5	6.0	4.5
6*	23.0	3.5	4.0

* Determined following transfusion of normal donor-labeled S-35 plasma.

Gofman et al.; fibrinogen: method of Surgener et al. Homogeneity of plasma fraction samples taken for measurement of specific activity has in each subject been repeatedly appraised by electrophoresis; 80 to 100 per cent homogeneity has been found.

All subjects have been studied in the steady state. Rate of loss of isotope from the plasma fraction has been interpreted as reflecting the life-span of the specific protein molecules. In twelve experiments acceptable data have been obtained variously for albumin, beta-1-lipoprotein or Cohn I + III fraction, and fibrinogen. Values for gamma globulin have thus far been erratic in distribution.

MECHANISM OF PIGMENTATION IN ADDISON'S DISEASE. Aaron Bunsen Lerner, Thomas B. Fitzpatrick* and Kazuo Shizume. Division of Dermatology, Univ. Oregon Medical School, Portland, Ore.

The various theories advanced to explain the increased melanin pigmentation found in Addison's disease will be reviewed. Clinical and experimental evidence will be presented to show

that the hyperpigmentation is probably due to an increase in the release of the melanocyte-stimulating hormone (MSH) from the pituitary gland as a result of a decrease in adrenal cortical function. Administration of MSH to normal persons produces an increase in pigmentation. MSH is a distinct hormone which, so far as is known, has no function other than that of stimulating the melanin-forming cells, the melanocytes.

COMPARISON OF TYROSINASE ACTIVITY IN NORMAL AND NEOPLASTIC HUMAN PIGMENT CELLS USING RADIOACTIVE TYROSINE. Thomas B. Fitzpatrick,* Atushi Kukita and Aaron Bunsen Lerner. Div. Dermatology, Univ. Oregon Medical School, Portland, Ore.

On the basis of previously reported studies using histochemical and biochemical technics, it has been shown that the tyrosinase system exists in an inactive state in normal human white skin and in dermal nevi but in an active, functioning state in normal human skin irradiated with ultraviolet radiant energy and in mammalian and human malignant melanomas. The existing histochemical technics for tyrosinase activity in very small amounts of tissue are not applicable to pigmented tissue such as pigmented nevi. For determination of tyrosinase in small amounts of pigmented tissue, radioactive histochemical and cytochemical technics have been developed. Tyrosine is converted into an insoluble melanin in the cytoplasm of the cell containing tyrosinase. Tyrosine labeled with carbon 14 is incubated with the tissue; and in those cells containing an active or functioning tyrosinase system, labeled tyrosine is converted to labeled melanin which precipitates at the site of formation. Since radioactive tyrosine is soluble in water and radioactive melanin is insoluble in water, it is possible to free the incubated tissues of radioactive tyrosine and measure only the radioactive melanin formed in the cytoplasm of the melanocyte.

A more recently developed technic utilizes homogenates or cell suspensions on a 18 by 18 mm. glass cover slide. The cell suspension is fixed with 70 per cent alcohol which inactivates cytochrome oxidase but not tyrosinase. The fixed dried cell suspension is then incubated in specially designed plastic glass holders in radioactive tyrosine for six hours at 37°C. With this technic we have obtained about 80 per cent conversion of the tyrosine to melanin with

melanoma cell suspensions. Pigmented nevi cell suspensions convert only a small proportion of radioactive tyrosine to melanin.

SOME PROPERTIES OF AN ANTI-MITOCHONDRIAL GAMMA GLOBULIN. *H. S. Mason.* Depts. Biochemistry and Dermatology, Univ. Oregon Medical School, Portland, Ore.

When crude homogenates of rat tissue are injected into rabbits, antitissue sera are elicited (Pressman et al.). The antibody proteins of these antisera have, however, a strong tendency when injected into the intact rat to localize in other tissues as well as that used as antigen. In the present study we have attempted to prepare tissue-specific antisera using intracellular particulates as antigen. Chemically unique intracellular granules, the mitochondrial melanin granules of the Harding-Passey mouse melanoma, were isolated by differential centrifugation of tumor homogenates and employed as an antigen in rabbits in accordance with the Freund adjuvant technic. Anti-melanin granule sera, and from these, anti-melanin granule gamma globulin fractions, were obtained. These antibodies strongly agglutinated suspensions of melanin granules in contrast to sera or gamma globulin from the same animals prior to immunization. No cross-agglutinations were obtained with corresponding fractions of liver, lung, heart, aorta, skin or mouse amelanotic melanoma.

Anti-melanin granule gamma globulin was tagged with tracer quantities of radioiodine and its distribution pattern in mice bearing Harding-Passey melanomas was determined. Specific localization failed to occur, the (heterologous) antibody behaving as a foreign protein. The implications of this study with regard to tumor therapy by tagged anti-tissue sera will be discussed.

OBSERVATIONS WITH PITUITARY GROWTH HORMONE IN HUMAN SUBJECTS. *Laurance W. Kinsell,* Harry E. Balch, George D. Michaels, Gilbert C. Cochrane, George Fukayama, June Bilisoly and Marjorie Coelho.* Inst. Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

In contrast to earlier studies which were uniformly negative, growth hormone preparations administered to several human subjects during the past two years have produced significant evidence of growth stimulation in terms of retention of the constituents of protoplasm (nitrogen,

phosphorus, sulfur, potassium) and weight gain. To date, positive results have been obtained only when the hormonal material was administered by slow intravenous drip.

Administration of the material to diabetic subjects resulted in a significant increase in hyperglycemia and glycosuria. The qualitative pattern appears to be significantly different than the accentuation of diabetes which occurs when one administers ACTH to such subjects.

A study carried out with a recently received lot of growth hormone in a patient with dwarfism, associated with ovarian agenesis, was unrewarding because of considerable thyrotropin contamination. This was manifested by the appearance of severe discomfort sharply limited to the area of the thyroid gland, which appeared on the second day of administration and disappeared two days after administration was stopped. In association with this there was a very significant elevation in pulse rate and in oxygen consumption.

Under way at this time is a study in a male with advanced osteoporosis who is receiving material prepared in a somewhat different manner from any previously used. The results of this study will be reported subsequently.

It is apparent that many problems still exist in the preparation of pituitary growth hormone of predictable purity and biological activity.

IMPROVED METHOD FOR THE BIOASSAY OF THYROTROPIC HORMONE. *Francis S. Greenspan,* Joseph P. Kriss and Lincoln E. Moses (with the technical assistance of William Lew).*

The bioassay of thyrotropic hormone (TTH) using the uptake of radioactive phosphorus (P32) by the chick thyroid, as proposed by Besford, Crooke and Matthews, and by Lamberg, has been simplified and improved. Groups of ten one-day old white Leghorn cockerels receive TTH injected directly into the heart and, simultaneously, 20 microcuries of P32 intraperitoneally. Six hours later the animals are killed by decapitation. The thyroids are carefully dissected out, placed on small copper discs and beta radioactivity determined. The response is expressed as counts per second per thyroid per chick, and when the response is plotted against the logarithm of the dose, a linear relationship exists between 0.4 and 16 milliunits (0.0004 — 0.016 USP units) of a standard TTH preparation. Data will be presented to indicate that intracardiac injection of TTH increases the

sensitivity of the method about tenfold. Furthermore, the variability of the method has been decreased by not expressing the response as counts per mg. thyroid tissue, and by not correcting for the blood level of P32. Preliminary data indicate that the method is suitable for the measurement of TTH in human urine extracts.

STUDIES WITH LABELED THYROXINE AND TRIIODOTHYRONINE. *John R. Hogness,* Paul Van-Arsdel, Jr. and Margaret Berg.*

I^{131} -labelled L-thyroxine and triiodothyronine were administered intravenously to rats and at varying time intervals the animals were sacrificed. Specimens of liver, kidney and muscle were homogenized, digested with trypsin and extracted with butanol. The extract was passed through kieselguhr columns for purposes of separation of possible metabolic products. In animals given triiodothyronine no thyroxine was recovered from any of the tissues studied and, conversely, no triiodothyronine was recovered from animals injected with thyroxine.

In another experiment comparing the two substances, isolated rat diaphragms were incubated in buffered medium containing L-thyroxine or triiodothyronine, under controlled conditions, for varying periods of time. The radioactive compound was fixed to the muscle at a much more rapid rate in the case of triiodothyronine although the ultimate total uptake was the same in the case of both substances.

The urinary and fecal excretion of labelled L-thyroxine were studied in five groups of rats in altered states of thyroid function, consisting of (1) controls, (2) animals fed propylthiouracil, (3) thyroidectomized animals, (4) animals injected with large doses of L-thyroxine and (5) animals injected with thyrotropin. The most striking observations were (1) a fall in urinary radioiodine excretion and a rise in fecal excretion in animals fed propylthiouracil, (2) reduction in fecal excretion of I^{131} associated with a diminished fecal volume in thyroidectomized animals, (3) a marked increase, on the first day, of urinary and fecal I^{131} excretion in animals under thyroxine load and (4) an increase in fecal excretion on the first day of animals receiving TTH. The significance of these findings is discussed.

HYPOTHYROIDISM AND HYPERPLASIA OF THE THYROID IN PATIENTS TREATED WITH COBALTOUS CHLORIDE. *Joseph P. Kriss and William H. Carnes.*

JULY, 1954

Depts. Medicine and Pathology, Stanford Univ. School of Medicine, San Francisco, Calif.

During the course of a study of the effects of enteric-coated cobaltous chloride in patients with sickle cell anemia, visible goiters developed in two male children. One of the goiters was so firm and irregular as to suggest thyroid cancer. Further investigation of these cases revealed some clinical features of hypothyroidism, marked reductions in protein-bound iodine and radioactive iodine uptake and elevations of serum cholesterol. Incisional biopsy of the goiters showed marked diffuse hyperplasia. Clinical and laboratory recovery occurred within a few weeks after the cobaltous chloride was discontinued. Abnormalities of thyroid function and small goiters have also been noted in two additional cases but no biopsy has been taken. Another child with sickle cell anemia and a fifty-one year old woman with anemia associated with renal failure similarly treated with cobalt came to autopsy and revealed thyroid hyperplasia. The degree of correlation between thyroid dysfunction and serum cobalt levels will be reported. Possible mechanisms of the goitrogenic action of the drug will be discussed.

MEASUREMENT OF "TOTAL" CORTICOSTEROIDS AND 17-HYDROXYCORTICOSTEROIDS IN PLASMA. *Don H. Nelson* and George W. Calver.*

The determination of plasma 17-hydroxycorticosteroids has been very useful in measuring levels of circulating corticosteroids but has the disadvantage of measuring only one particular type of corticosteroid. Other corticosteroids which would not be measured are known to be secreted by the adrenal cortex. The determination of "total" corticosteroids with the color reaction of Gornall and MacDonald has therefore been applied to the method of Nelson and Samuels so that other corticosteroids can be determined at the same time that the 17-hydroxycorticosteroids are measured. Normal plasma levels of these compounds in a small group of normals is 27 gamma per cent as compared with a 17-hydroxycorticosteroid level of 13 gamma per cent. This difference is maintained or increased when ACTH or corticosterone is given to an experimental subject, but decreases following cortisone administration. Thus following ACTH administration both types of steroids were increased in the peripheral blood. When corticosterone was given the 17-

hydroxycorticosteroids made up a smaller part of the total than in the normal and when cortisone was given most of the circulating corticosteroid was of the 17-hydroxy type. This method and a similar procedure used for determining 17-hydroxycorticosteroids, "total" corticosteroids and formaldehydogenic steroids in urine have been used in the investigation of the fate of administered corticosteroids.

DYNAMICS OF ADRENAL CORTICAL ACTIVATION IN DIFFERENT FUNCTIONAL STATES. *P. H. Forsham,* F. O. Kolb, G. W. Liddle and D. Island*, Metabolic Unit, Univ. California School of Medicine, San Francisco, Calif.

A simple test for urinary 17-hydroxycorticoids which may be run at a clinical level has been worked out. It shows a normal twenty-four-hour "F" equivalent of 9.5 ± 4 mg. for normal males (95 per cent probability limit) and 6.5 ± 2.5 mg. for females (95 per cent probability limit). The quantitative estimation of adrenal cortical responsiveness has been studied. Normals, patients with Addison's and Cushing's disease show a slight overlap of the control values. However, following stimulation with a standard intravenous ACTH test (25 USP units over eight hours) a clear-cut differentiation may be observed by the twenty-four-hour output of 17-hydroxycorticoids. In a case of adrenal carcinoma there was no elevation in contrast to a rise in cases of bilateral hyperplasia and a benign adenoma. Inhibition of the adrenal cortex by cortisone was not obtained in the case of adrenal carcinoma. In three cases with normal adrenal responses the adrenal involution was not prevented by the concurrent administration of methylandrostenediol, in contrast to reported observations in rats.

EXPERIENCES WITH THE USE OF ADRENAL STEROIDS AND CORTICOTROPIN IN CLINICAL CONDITIONS OF STRESS. *J. M. Rukes, J. H. Bruce, M. Galante and P. H. Forsham.** Metabolic Unit, Cancer Research Inst., and Dept. Surgery, Univ. California School of Medicine, San Francisco, Calif.

The metabolic reactions to the stress of surgery may be stimulated prematurely by the preoperative use of ACTH or the cortisones and may be artificially continued thereafter. This fact has been utilized in the pre- and postoperative management of twenty-five cases of bilateral adrenalectomy for metastatic carcinoma of the

breast. ACTH has been used in debilitated patients and in a case of thrombocytopenic purpura. Intravenous hydrocortisone, 100 mg. dissolved freshly in 1,000 ml. of 5 per cent D/W, has proved most useful in a series of patients showing oliguria and low blood pressure following major surgery, including valvulotomy and endarterectomy. There have been no untoward side effects or interference with wound healing by observing the following: (1) limiting therapy to five to seven days; (2) rapid reduction from maximal dose to maintenance or discontinuance; (3) salt restriction; (4) no use of DCA as long as high dosage of the cortisone was employed; (5) giving corticotropin gel for the last two to three days of cortisone therapy and rapid reduction thereafter to minimize the "let-down" due to adrenal cortical involution. Illustrative cases, including the estimation of urinary 17-hydroxycorticoids, will be presented.

ADRENAL CORTICAL FUNCTION AND ACTH THERAPY IN PATIENTS WITH SYDENHAM'S CHOREA. *Lorin E. Ainger, Robert S. Ely, Alan K. Done and Vincent C. Kelley.**

The lack of demonstrable biochemical abnormalities in patients with Sydenham's chorea, despite the intimate clinical relationship between this syndrome and rheumatic fever, long has puzzled investigators.

Preliminary observations demonstrating alterations in serum levels of hyaluronidase inhibitor, non-glucosamine polysaccharides, mucoproteins and hexosamines have been reported previously from our laboratories. In the present report these observations have been confirmed and extended. Likewise, it has been shown that these acute phase reactants are related to adrenal cortical function. Therefore, when technics for direct measurement of blood levels of pituitary-adrenal hormones became available these measurements were made in patients with chorea. The mean plasma 17-hydroxycorticosteroid level in thirty patients with chorea was 6 μ g. per cent compared with a normal mean value of 12 μ g. per cent. In some of these patients elevations of circulating endogenous ACTH levels were demonstrated. Thus abnormally low 17-hydroxycorticosteroid levels and abnormally high endogenous ACTH levels occur simultaneously. This is interpreted as relative adrenal insufficiency. Despite this relative insufficiency these patients respond to exogenous ACTH by increases in 17-hydroxy-

corticosteroid plasma levels comparable to the increases observed in controls; thus the adrenal cortex is capable of adequate steroid secretion under appropriate stimulation. That these hormonal abnormalities could be corrected by exogenous ACTH administration suggested that ACTH therapy in chorea might prove efficacious. The clinical and laboratory results of fourteen courses of hormone therapy will be presented. In all but one, dramatic clinical improvement occurred, but in none was there a sudden cessation of *all* choreiform activity.

The data presented indicate that extension of these studies may enhance our understanding of the pathogenesis of this disease and supply rational basis for therapy.

INFLUENCE OF CORTISONE ON THE EFFICACY OF ANTIBIOTIC THERAPY IN EXPERIMENTAL INFECTIONS. *Ernest Jawetz.** Univ. California School of Medicine, San Francisco, Calif.

Cortisone tends to promote the activation and spread of microbial infection in man and experimental animals. When cortisone is used clinically in the presence of infection, antibiotic agents are often administered to "cover" this harmful effect. The question arises, however, whether the interference of cortisone with the natural defenses of the host might significantly impair the therapeutic efficacy of antimicrobial agents.

To investigate this possibility experiments were carried out in two subacute infections of mice. The dose of cortisone employed (0.15 mg. injected subcutaneously daily for five days) permitted normal weight gain and did not result in any mortality in uninfected animals. Animals were infected intramuscularly with 10-2000 LD₅₀ of either a hemolytic *Streptococcus* or a *Klebsiella*. All untreated animals succumbed in from two to six days. Cortisone injections were begun six hours after infection. Treatment with either penicillin or aureomycin was administered according to various time-dose schedules throughout the period of cortisone injections to groups of twenty-five or more animals. Deaths of animals were recorded for two weeks.

The results indicated that cortisone interfered with the therapeutic effect of the antibiotics. For example, aureomycin 2.4 mg. per mouse, given in a period of five days, cured 72 per cent of animals with a *Klebsiella* infection, while the addition of cortisone reduced the cure rate to 12 per cent ($P = 0.00$). This interfering effect of cortisone was more marked with barely curative

amounts of bacteriostatic drugs than with large doses of bactericidal agents. To some extent, the cortisone effect was overcome by a large excess of the antibiotics. Quantitative aspects of this phenomenon, its possible mechanism and clinical implications of these results will be considered.

QUANTITATIVE EVALUATION OF TISSUE GROWTH. *George D. Michaels, Etsuko Osawa, Rosalie French and Laurance W. Kinsell.** Inst. Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

A variety of methods has been described for quantitative evaluation of wound healing. None has been satisfactory.

During the past five years in this laboratory S-35 labeled methionine has been administered to animals in whom varieties of experimental wounds have been produced. Initially, incorporation of the S-35 into the wound tissue was used as the sole index of tissue regeneration. More recently, in addition to specific activity of S-35 the following constituents of an experimental "wound" made by implanting sterile gauze pledgets beneath the skin of experimental animals have been determined quantitatively: sulfur, nitrogen and phosphorus. Also the histologic evaluation of the experimental "wounds" has been carried out. Data obtained to date indicate that this technic: (1) represents a reproducible quantitative procedure for evaluation of nuclear and extranuclear growth; (2) constitutes a quantitative technic for evaluating the local and systemic effects of hormonal agents which inhibit or stimulate tissue growth.

Included in the report will be data obtained with local and systemic administration of corticoids, anabolic steroids and pituitary growth hormone.

DETERMINATION OF ALVEOLAR CO₂ WITH A PORTABLE RAPID INFRA-RED ANALYSER. *Clarence R. Collier, John E. Affeldt and Andrew F. Farr.** From the Rancho Los Amigos Respiratory Center for Poliomyelitis, Hondo, Calif., and Dept. Internal Medicine, College of Medical Evangelists, Los Angeles, Calif.

The development of a portable, rapid, infra-red CO₂ analyser has made the determination of the alveolar CO₂ concentration readily available as a clinical test. Because the concentration of alveolar CO₂ varies with both "space and time," only an approximation of mean alveolar CO₂ can be obtained by any method.

Measurement of arterial P_{CO_2} is undoubtedly the most accurate approximation of alveolar CO_2 but is both difficult and time-consuming.

Any method to be ideal for the determination of alveolar CO_2 must: (1) be easily used with untrained subjects, (2) not interfere with normal breathing, (3) provide continuous measurement as well as "spot checks," (4) require minimal time and effort, (5) detect contamination with dead space air and (6) be sufficiently accurate for clinical use.

The rapid, infra-red CO_2 analyser is capable of fulfilling all these requirements when samples are drawn from the expired air stream by means of a small polyethylene catheter. The mean error of eighteen experiments with the catheter technic compared to simultaneous arterial P_{CO_2} determinations is -1.0 mm. Hg. A total of forty-one comparisons of simultaneous infra-red and arterial P_{CO_2} values using both the catheter technic and other sampling methods show good correlation.

This measurement is now extensively used clinically as a guide to ideal respirator settings for patients with chronic respiratory paralysis due to poliomyelitis. It is a valuable test since it can readily detect even slight hypo- or hyperventilation.

ON THE ORIGIN OF THE HEART BEAT. *Allan J. Brady and Hans H. Hecht.* * Dept. Medicine, Univ. Utah College of Medicine, Salt Lake City, Utah.

The sinus region of eighteen turtle hearts was explored by the use of capillary micro-electrodes having an external tip diameter of less than 0.5 micron. Membrane resting and membrane action potentials were recorded from single fibers of the area thought to originate the excitation wave and usually situated just to the right of the midline of the sinus venosus. Records from these fibers were compared to control observations obtained from auricular and ventricular regions of the same preparation. In the successful experiments "prepotentials" were obtained that preceded the event of cellular depolarization. These were of two types. One consisted of a slow decrease in membrane resting potential during electrical diastole. The second was a "pre-systolic" potential of shorter duration immediately preceding the rapid depolarization of the pacemaker cell. The duration of action potentials in these experiments were similar when recorded from the sinus region, auricular or ventricular tissue. An exponential relationship

existed between the action potential duration and temperature.

It is suggested that the prepotentials are characteristic for pacemaker regions but may be recorded only if the electrode is inserted into the fibers of the sinus region that originate the action current. The gradual diastolic or the rapid presystolic loss of membrane potential found in these experiments may represent inability of the fiber to maintain a steady resting diastolic potential across the membrane: the membrane leaks and firing of the cell occurs spontaneously when a critical drop in resting potential has occurred. This amounts to 10 to 20 per cent of the total membrane potential.

SERIAL ROENTGENOKYMOGRAMS IN ACUTE MYOCARDIAL INFARCTION. *J. J. Sampson,* B. Solomon, A. A. Goetz, L. Felton and B. Axelrad.* Depts. Medicine and Roentgenology, Mount Zion Hospital, San Francisco, Calif.

Twenty-six patients with acute myocardial infarction were studied by serial roentgenokymograms taken in bed by a modification of the Leibel-Florsheim Model K3 Multiple Slit Kymograph. Fourteen had initial records taken within twenty-four hours of the clinical onset of the attack, and successive records were generally obtained daily for four days, and every two to five days for two to four weeks. Detailed studies and tracings were made of the records by photographing them and projecting the images on a screen at a distance of 15 to 20 feet.

Systolic expansion of the left ventricle was observed in seven patients and varied in duration from less than one day to over twenty-one days. This phenomenon developed in certain patients with recurrent cardiac pain, pallor and weakness, without other objective signs of circulatory failure, as well as in those with shock or heart failure, and was observed to persist in some instances after clinical recovery. Other abnormal ventricular phenomena observed were (1) delayed onset of systolic contraction, (2) left systolic expansion, (3) abnormal patterns or absence of diastolic expansion curves and (4) flattening of all waves generally observed in the apical region.

Two patients with shock, treated with nor-epinephrine, exhibited abnormal apical flattening of waves. One recovered a normal pattern during infusion after the blood pressure was sustained at an effective level for twenty-four hours. The other patient's blood pressure was

restored to a satisfactory level, but the electrokymographic pattern remained abnormal and the patient died suddenly one day later. In one instance the clinical and electrocardiographic signs of a secondary infarct followed a day after the appearance of new ventricular electrokymographic abnormalities. In one case the area of ballooning or systolic expansion of the left ventricle apparently exceeded the area of posterolateral infarction demonstrated at autopsy. The area of systolic expansion or other abnormalities of the roentgenkymogram seemed greater in other cases than would be expected from electrocardiographic localization of the infarcts.

This bedside technic with reproducible results, while presenting occasional difficulties in interpretation of records, gives objective evidence of mechanical impairment of the myocardium during the fluctuating course of early myocardial infarction.

STUDY OF THE PHYSIOLOGIC CLOSURE OF THE DUCTUS ARTERIOSUS IN NEWBORN INFANTS. *Frederic L. Eldridge, Herbert N. Hultgren* and Mary E. Wigmore.* Dept. Medicine, Stanford Univ. School of Medicine, San Francisco, Calif.

The exact time of functional closure of the ductus arteriosus in the normal human infant has never been determined, although animal experiments have suggested closure immediately after birth. In order to determine this, capillary blood samples were obtained, with minimal exposure to air, from the previously warmed right hand and foot of twenty-seven normal newborn infants during the first five days of life. These samples were analyzed by the Roughton-Scholander microtechnic for their oxygen content and capacity. In all but two of the twenty-seven infants blood samples from the right hand had oxygen saturations of 90 per cent or more. In infants one to three hours after birth the oxygen saturation of blood from the foot was significantly lower than that from the hand in nine of eleven cases studied, indicating the presence of a veno-arterial shunt to the lower part of the body. In infants three to seventy-two hours after birth five of ten cases showed a foot saturation significantly lower than that of the right hand. None of the six infants over three days of age showed any significant difference in saturation between right hand and foot.

These findings indicate that the ductus arteriosus is patent and that a veno-arterial

shunt occurs in most infants under the age of three hours; that this condition may persist in nearly 50 per cent of infants up to the age of three days; and that in infants over this age the ductus arteriosus is probably closed to the passage of blood, or else the shunt has become arteriovenous due to a decrease in pulmonary vascular resistance and therefore not measurable by this technic.

MUSCULOSKELETAL CIRCULATORY RATES DETERMINED WITH I^{131} HUMAN SERUM ALBUMIN. *Rex L. Huff, George Bogardus, Harold Broadbrooks and David Feller.* Depts. Medicine and Surgery, Univ. of Washington School of Medicine, and the Radioisotope Unit, V. A. Hospital, Seattle, Wash.

A method has been devised for measuring blood flow rates in the legs and feet of patients. Values obtained by this method are similar to those obtained by plethysmograph and by nitrogen elimination. This method using I^{131} human serum albumin (HSA) is thought simple and practical enough for clinical application.

After a single intravenous injection of a small amount of I^{131} HSA, the counting rate over the feet and legs rises as a function of time. This rise is usually in the form of a simple growth curve, the half times of which vary from one-half to six minutes. In order to evaluate geometry of counting, water-tight, thin-walled casts were made of patients' legs and feet. These casts were then filled with I^{131} solution so that identical counting rates were obtained at a corresponding position on the cast as on the legs at the time of equilibrium counting rate. Since the specific activity of the blood was known, an equivalent of grams of blood per 100 gm. of tissue could be calculated. The distribution of blood among skin, muscle and bone was measured in amputated extremities, the blood of which had been previously tagged with I^{131} HSA. Just before amputation a tourniquet was vigorously and quickly applied. These data show slight but not marked differences in the quantity of blood per unit weight of the various tissues. Using the value of blood per unit tissue and the measured time constant, flow rates were calculated on the basis of a two-compartment model, the compartments having equal volumes. By this method it is thought possible to assess bone and muscle perfusion rates separately.

Data of blood flow rates will be given of patients with arteriosclerosis obliterans, thrombo-

angiitis obliterans, myxedema, congestive failure on the basis of chronic valvular diseases and arteriosclerotic heart disease.

AUSCULTATORY DETERMINATION OF ARTERIAL PRESSURE AT WRIST AND ANKLE. *David A. Ryland* and Samuel H. Boyer, IV.* Stanford Univ. School of Medicine, San Francisco, Calif.

Because the usual methods yield erroneously high values for arterial pressure when the standard cuff is applied to thighs or large arms, a wider cuff has been recommended officially. We have found, however, that the standard cuff is satisfactory on the legs as well as on the arms of obese subjects when it is applied just proximal to ankle or wrist. Auscultation at the appropriate artery is facilitated by removal of the stethoscope bell's plastic portion. The method is practicable in all but hypotensive patients, in whom systolic pressure may be determined by palpation.

In recumbent normal subjects, systolic pressure by auscultation was on the average 6 mm. Hg lower in the radial than in the brachial artery; diastolic pressure (muffling) was 6 mm. Hg higher. The deviation was less than 20 mm. Hg in 90 per cent of observations on fifty-three individuals (not simultaneous) with brachial pressure under 180/100 mm. Hg. In the posterior tibial, systolic pressure was 2 mm. Hg and diastolic pressure 5 mm. Hg above brachial levels; dorsalis pedis levels were comparable.

In twenty frankly hypertensive patients, mean pressure relationships were in the same range, sometimes with greater individual variations. With aortic insufficiency, findings were similar but for striking elevation of posterior tibial systolic pressure. Differences between muffling and disappearance of sound were less at the wrist than at the brachial artery. In three patients with mammoth obesity radial and ankle pressures were far below brachial ones (20 to 85 mm. Hg diastolic, 60 to 140 mm. Hg systolic).

CARDIOVASCULAR AND RENAL RESPONSES TO THE COMBINATION OF HEXAMETHONIUM AND 1-HYDRAZINOPHTHALAZINE IN HYPERTENSIVE SUBJECTS. *David H. Stein, Homer R. Warner and Hans H. Hecht.** Dept. Medicine, Univ. Utah College of Medicine, Salt Lake City, Utah.

Fourteen hypertensive subjects were studied in order to evaluate cardiovascular and renal adjustments to intravenous 1-hydrazinophthalazine alone, and after the prior administration intravenously, of hexamethonium. Cardiac out-

puts were determined by oxygen consumptions and A-V oxygen differences. Standard renal clearance technics for inulin and p-aminohippuric acid were used.

The following observations were made: (1) Cardiac output increased in all of seven patients studied after 0.25 - 0.50 mg./kg. of 1-hydrazinophthalazine. (2) Four of the patients were given 10 to 12.5 mg. of hexamethonium ion thirty to forty-five minutes before the 1-hydrazinophthalazine. The expected rise in cardiac output from apresoline® could be prevented by this procedure. (3) Only those patients with normal or nearly normal resting renal plasma flow (three of eight patients studied) experienced considerable increases in renal blood flow after 1-hydrazinophthalazine 0.20 to 0.40 mg./kg. (4) Hexamethonium (10 to 12.5 mg. of the ion) administered thirty to forty-five minutes before the 1-hydrazinophthalazine did not prevent the considerable increase in renal plasma flow following apresoline.

In summary, the effects of apresoline on cardiac output appear to depend on a central stimulating action, since they can be prevented by autonomic blocking agents. The increase in renal blood flow, whenever present, appears to be independent of systemic blood flow. The clinical use of apresoline in combination with hexamethonium may therefore have a rational basis.

BEDSIDE METHOD FOR THE DETERMINATION OF TOTAL BASE IN SERUM. *Belding H. Scribner* and H. Thomas Wiegert.*

Since serum total base reflects serum sodium, a bedside total base method could be used as a substitute for the sodium determination.

Serum is run through a column of cation exchange resin which exchanges cations for H⁺. Part of this H⁺ reacts with serum bicarbonate which escapes as CO₂. The remainder reacts with other serum buffers and is measured by titrating the serum back to pH 7.4. The total base equals this titration plus the serum bicarbonate concentration which can be determined by another bedside method. This total base method employs a resin column formed in the barrel of a tuberculin syringe. The samples are measured and titrated with tuberculin syringes. The procedure takes about five minutes and will be demonstrated in a motion picture. The precision of the method is ± 1 mEq./L. Total base was determined in twenty-six specimens.

Results were compared with totals of concentrations of cations determined individually. The standard deviation was 1.3 mEq./L. The difference between the means was minus 0.3 mEq./L. In a variety of patients, variations in total base correlated closely with variations in serum sodium and serum osmolarity as measured by freezing point depression. By subtracting eleven from the value for total base, serum sodium could be predicted. On twenty-six specimens the standard deviation was 1.2 mEq./L.

SODIUM CONTENT OF GASTROINTESTINAL SECRETIONS AND THE PENETRATION OF RADIOSODIUM INTO THE GASTROINTESTINAL TRACT. *I. S. Edelman and N. J. Sweet.* Dept. Medicine, California School of Medicine, San Francisco, Calif.

Previous studies have largely ignored the pool of water and electrolytes within the lumen of the gastrointestinal tract in the estimation of shifts of water and electrolytes within the body. In this study we have measured the fraction of total exchangeable sodium within the lumen of the gastrointestinal tract. Forty rabbit experiments have been carried out to date. Following the administration of Na^{24}Cl , samples of blood and urine were obtained and the gastrointestinal tracts removed, from the cardia of the stomach to the mid-transverse colon. These animals were studied with fasting periods varying from twelve to forty hours. In all instances a twenty-four-hour period of isotope equilibrium was allowed.

The following results were obtained: (1) Intraluminal G-I tract sodium content averaged 13.5 per cent of the total body sodium, with a range of 10.2 to 17.5 per cent. (2) Distribution equilibrium of the injected radiosodium was achieved in twenty-four hours. The partition of sodium in the gastrointestinal tract expressed as per cent of total exchangeable sodium was found to be as follows: (a) stomach = 0.7 per cent (range 0.4 to 1.0 per cent), (b) small intestine = 3.0 per cent (range 2.3 to 3.5 per cent), (c) cecum and proximal transverse colon = 9.5 per cent (range 7.3 to 11.0 per cent). (3) There is no apparent difference in the gastrointestinal sodium content or the total exchangeable sodium in the male rabbit as compared to the female (non-pregnant) rabbit. (4) In the three groups with fasting periods of twelve hours, twenty-four hours and thirty-six hours, respectively, there were no significant differences in intraluminal gastrointestinal sodium contents or its distribution along the G-I

tract. (5) The twenty-four-hour stool sodium excretions were negligible.

These data indicate that a significant proportion of the total body sodium pool is within the lumen of the gastrointestinal tract.

EFFECT OF ACUTE URINARY SUPPRESSION ON THE PLASMA VOLUME, HEMATOCRIT AND ELECTROLYTES IN THE DOG. *Harold Brown,* A. A. Iliya and P. B. Price.* Veterans Hospital and Depts. Medicine and Surgery, Salt Lake City, Utah.

Daily estimations of the plasma volume, hematocrit, sodium, potassium, chloride and inorganic phosphorus were made in eighteen dogs rendered anuric by ligation of the ureters. Six of the animals were allowed food and fluids while the other twelve were starved. Except for weight changes and plasma sodium values, the results in the two groups were the same and will be discussed together. Plasma volumes were estimated by the Evans blue and the radioactive iodine tagged albumin technics.

There was a steady rise in the plasma volume to a value averaging about 30 per cent above and a drop in the hematocrit to about 25 per cent below the preoperative values. The electrolytes followed the expected pattern in uremia with a marked rise in the levels of potassium and inorganic phosphorus and a moderate drop in the plasma chloride level. In the starved animals there was no significant change in the plasma sodium level, which dropped an average of 11 mEq./L. in the group allowed food and water. The latter group also showed no significant weight loss. Although the "fed" animals died sooner, most of the animals were dead by the fifth postoperative day of potassium intoxication and/or pulmonary edema. The implications of these findings in relation to the therapy of acute renal failure and the mechanism of the anemia of acute uremia will be discussed.

EXPERIMENTAL STUDIES ON THE MECHANISM OF MERCURIAL DIURESIS. *Chester Hyman, Ernest Geiger and Tatsuo Kimura.* Dept. Physiology, School of Medicine, Univ. Southern California, Los Angeles, Calif.

It has been reported that mercurial diuretics orally administered are consistently less active than when given parenterally. This could reflect inadequate absorption of the compound from the gut, or inactivation by the liver. In some earlier studies it was shown that the concentration of mercury in the livers of rats was greater

when the animals were fed a mercurial diuretic than when injected with corresponding amounts of the same diuretic. In rabbit preparations in which the rate of kidney urine formation was measured directly, we could find no significant difference between the diuresis resulting from infusion of mercurhydrin into the ear vein or into the portal vein. It therefore seems probable that the difference in clinical efficacy noted above results from impeded absorption of the compound from the gastrointestinal tract.

Certain clinical observations suggest a relationship between bile and urine formation. The suggestion that mercurial diuretics are less effective in patients with bile fistulas has been confirmed in rabbit preparations. Equal doses of mercurhydrin give about one-third to one-half as great a diuresis in the bile fistula animals as in normals. An attempt has been made to discover a relationship between urine and bile formation. In normal animals administration of a choleric agent does not alter the rate of urine formation; likewise, administration of a diuretic does not diminish or increase the rate of bile formation. We have not been able to confirm the reported diuretic effect of decholin *per se*, but administration of this hydrocholeric agent after the maximum mercurial induced diuresis leads to a re-establishment of the diuresis. The mechanism of this augmentation is still not clear. We have not been able to show that introduction of bile into the gut could lead to an augmented diuresis. Neither could we demonstrate that an increased intrahepatic biliary pressure could lead to augmentation of mercurial diuresis.

Studies on the electrolyte composition of the urine and bile under a variety of circumstances indicate that mercurials increase the rate of sodium excretion; that the restored diuresis following on decholin administration is likewise associated with increased sodium output; and finally, that the decholin choleresis is not accompanied by an increased sodium output.

TREATMENT OF THE NEPHROTIC SYNDROME IN CHILDREN WITH 10 PER CENT SALT-FREE DEXTRAN OR GELATIN, INDUCTION OF DIURESIS AND EFFECTS OF PLASMA PROTEINS. *Robert A. Aldrich,* Anne Perley, and Tyra Hutchens.*

Repeated intravenous administration of 10 per cent salt-free dextran or gelatin to children with the nephrotic syndrome induces marked diuresis and an absolute reduction in the total plasma protein. These effects will be illustrated by data

obtained from four consecutive patients. The effect on plasma protein was further investigated by measuring plasma volume with radioiodinated human serum albumin and quantitation of urinary protein loss.

The fall in total plasma protein cannot be explained by plasma volume expansion alone. In one individual the plasma volume was 109 per cent of the pretreatment figure when the plasma protein was only 50 per cent of the initial level. Later, following further treatment, the total plasma protein fell further to 32 per cent but the plasma volume at this time was 111 per cent of the original figure. Another patient showed plasma protein reduction to 54 per cent with a plasma volume which measured 115 per cent of the initial amount. After further treatment the plasma protein fell to 45 per cent but the plasma volume was practically identical with that obtained at the outset.

Augmented urinary protein loss is not the cause of the reduced plasma protein. In one of the above patients urinary protein was chemically quantitated before, during and after treatment; there was no significant change.

Two of the four children are in spontaneous remission at present. The practical application of this technic and the implication of these observations will be discussed.

PATHOPHYSIOLOGY IN PULMONARY HYPERTENSION OF UNKNOWN ETIOLOGY. *S. Gilbert Blount, Jr. and Malcolm C. McCord.* Univ. Colorado School of Medicine, Denver, Colo.

Nine patients with elevated pulmonary artery pressure of obscure origin have been evaluated by cardiac catheterization with pathologic correlation in three instances.

The group consisted of eight females and one male with an age range of from ten to fifty-five years. The history, physical examination, electrocardiogram and fluoroscopy were indicative of pulmonary hypertension and right ventricular hypertrophy. There was a significant elevation of the pulmonary artery pressure in all patients with mean resting pressures ranging from 41 mm. Hg to 99 mm. Hg. A further increment occurred following mild exercise, rising in one patient from a mean resting level of 87 mm. Hg to a mean exercise level of 131 mm. Hg. Pulmonary "capillary" pressures were obtained in six patients and fell within normal limits, both at rest and following exercise in three patients. In two patients in congestive failure the "capil-

lary" pressures were moderately elevated. Thus the pulmonary "arteriolar" resistance was markedly elevated, indicating obstruction proximal to the pulmonary "capillary" bed.

Analysis of multiple blood samples revealed no evidence of a left to right shunt in these patients. Peripheral arterial oxygen unsaturation was present in five of the nine patients. The cardiac output was uniformly decreased and showed no significant change following exercise. The mean resting cardiac index was 2.16 L. and following exercise the mean was but 2.24 L.

Postmortem examination in three patients revealed dilatation and hypertrophy of the right ventricle and right atrium. There was no evidence of congenital cardiovascular defects. The large pulmonary arteries were dilated and demonstrated atheromatous plaques. Microscopic examination of the lungs showed medial hypertrophy and intimal proliferation of the smaller pulmonary arteries.

CORRELATION OF MECHANICAL, X-RAY DIFFRACTION AND ELECTRON MICROSCOPE PROPERTIES OF THE AGING AORTA. *Hans H. Zinsser,* John Leonard, Hugh Edmondson* and Richard Baker.* Dept. Surgery, Univ. Southern California School of Medicine, Los Angeles, Calif.

Fifteen samples of aortic media have been analyzed simultaneously by several methods. Progressive increase in non-Hookian elastic constant occurs with increasing age. This elastic constant is increased by lowering of the salt concentration, with some increase in hysteresis. Hyaluronidase diminishes the elastic constant of the aged specimens over thirty, and increases the elastic constant of premature stillbirth, with corresponding but much smaller changes in hysteresis. Successive annular arrangement of elastic fibers throughout the media has been demonstrated by three dimensional reconstruction of light microscope sections. Electron microscope studies show increasing opacity to electrons throughout the ground substance and within the substance of the elastic fibrils. Even with ultra-thin sectioning, no fine structure has been detected in the elastic fibrils down to 30 Ångströms. Cubic crystals ranging in size from 0.1 to 1.0 μ . with an electron diffraction pattern indicating a repeating unit of approximately 1.8 Ångströms are prominent in the older specimens. X-ray diffraction at all ages shows a new pattern not characteristic of collagen, smooth muscle or a variety of organic and

inorganic salts, with a long spacing of 16.8 Ångströms, and other spacings closely approximating those found in monocalcium diglutamate. The suspicion that some trivalent metal is concerned with the emergency of this pattern with increasing age is borne out by emission spectrography in progress.

TRANSVAGINAL PELVIOSCOPY—OBSERVATIONS ON OVULATION IN THE HUMAN CORRELATED WITH THE BASAL BODY TEMPERATURE CURVE. *A. R. Abarbanel.** Depts. Obstetrics and Gynecology, College of Medical Evangelists, Los Angeles, Calif.

The ovarian findings in 250 women pelviscoped during the menstrual cycle, during which an accurate basal body temperature (B.B.T.) curve was kept, were correlated. Evidence of ovulation was observed in 22 per cent on the day of the low point just before the sustained temperature rise, while on the next day (LP plus one) 68 per cent had an early corpus luteum. On day LP plus 2 some three out of four had a corpus luteum even though the B.B.T. curve disclosed a distinct rise. Further study revealed that a corpus luteum was absent in almost 10 per cent even though a typical diphasic curve was evident.

Equally significant is the fact that although spermatozoa can most easily penetrate the cervical mucus in great numbers on the day of the low point, ovulation does not necessarily occur within the next forty-eight hours. Consequently, conception may fail to occur if ovulation does not occur at the time of greatest sperm migration through the cervical mucus. Collateral evidence supports the claim that this syndrome can appropriately be called asynchronous ovulation.

ALTERATIONS IN THE STATE OF DIABETES INSIPIDUS RESULTING FROM CO-EXISTENT HYPOFUNCTION OF THE ANTERIOR PITUITARY AND ADRENAL CORTEX; STUDIES ON A CASE OF DIFFUSE MENINGIOMATOSIS. *A. W. Bagnall, C. McIver, D. K. Ford and R. A. Palmer.* Vancouver, B. C.

A rare condition, diffuse meningiomas, resulting in at least partial destruction of the anterior as well as the posterior portions of the pituitary gland, presented an opportunity to study certain body functions, particularly the handling of metabolic solutes by the kidneys, in diabetes insipidus.

By measuring the urine volume, the output and concentration of urinary solutes (by freezing-point determinations) during periods of low and high intake of solutes, with and without the administration of cortisone, the following observations have been made: 1) Co-existing anterior hypopituitarism may completely "mask" diabetes insipidus. 2) The urine volume in diabetes insipidus varies directly with the demand on the kidneys to excrete solute. 3) In diabetes insipidus "masked" by co-existing anterior pituitary hypofunction the administration of maintenance doses of cortisone increases the urine volume by restoring the sense of well being and the appetite. This leads to a greater intake of protein and other solutes which is followed by an increased output of urine solutes and a greater volume of poorly concentrated urine. 4) There is some indication that cortisone also increases the urine volume by a direct effect on the kidneys permitting greater dilution of the urine.

DIRECT EFFECT OF THYROTROPIC HORMONE (TSH) ON THE IODIDE CONCENTRATING MECHANISM OF THYROID TISSUE SLICES. *John L. Bakke* and Nancy Lawrence.* V. A. Hospital, and Dept. of Medicine, Univ. Washington, Seattle, Wash.

It has been shown that TSH will stimulate both the synthesis and release of thyroid hormone but it has not been shown that TSH will directly increase the collection and concentration of iodide in the thyroid inorganic iodide compartment. Vanderlaan, Halmi and others have reported that iodide collection is increased in the hypophysectomized rat after eight or more hours of TSH stimulation. However, their observations may be interpreted in the manner originally suggested by Rawson: The increased avidity of the thyroid for iodide is secondary to a depletion of glandular inorganic iodide consumed in increased hormone synthesis and release.

Direct TSH stimulation of the isolated iodide collecting compartment was measured by incubating beef thyroid slices in propylthiouracil media ($10^{-4}M$) containing I^{131} and TSH. The propylthiouracil blocked organic synthesis so that less than 1.5 per cent of the radioiodide was organically bound. Thus, iodide uptake was not influenced by hormone synthesis in these experiments.

In 1,290 observations it was demonstrated that TSH directly stimulated the collection of

inorganic iodide. TSH, 8×10^{-6} U.S.P. units ($0.1 \mu g.$), produced maximal stimulation. For example, after six hours' incubation control slices took up 39.7 ± 1.8 per cent (S.E.) and the stimulated slices took up 57.5 ± 1.8 per cent of the media iodide.

As little as 8×10^{-7} units of TSH have been detected by this method. This represents a simple, rapid, objectively measurable effect of TSH in quantities smaller than hitherto reported. The assay potentialities and the effects of adrenal hormones and serum iodide levels on the iodide collecting mechanism are being studied.

UNRESPONSIVENESS OF HUMAN MINERALOCORTICOID FUNCTION TO ACTH STIMULATION. *John L. Bakke* and Belding H. Scribner.** V. A. Hospital, and Dept. Medicine, Univ. Washington, Seattle, Wash.

A diagnosis of Addison's disease was established in two patients with a classical clinical picture, typical pigmentation, low 17-ketosteroid and 11-oxysteroid excretion, insulin hypersensitivity, abnormal Robinson-Kepler-Power test part 1 and 2, abnormal Soffer water test, and an abnormal Thorn eosinopenia test. However, both patients had a normal response to a Cutler-Power-Wilder test even though the low salt, high potassium stress was prolonged to seven days. This ability to conserve sodium and diurese potassium indicated normal mineralocorticoid response to electrolyte stress in spite of evident glucocorticoid and androgen deficiency.

Whether or not this intact isolated mineralocorticoid secretion would respond to ACTH stimulation was tested in two ways. ACTH, 5 units per hour, was administered intravenously over eight hours during a mild salt load provided by intravenous saline, 60 cc. per hour for twelve hours. The normal fall in urinary sodium excretion and increase in urinary potassium excretion did not occur. A similar test using ACTH-gel, 40 units, and oral sodium chloride, 0.6 gm. per hour, revealed the same abnormal unresponsiveness. These findings indicated that ACTH was unable to stimulate mineralocorticoid production in these two patients.

Thus human mineralocorticoid production appears to respond directly to electrolyte stress and is independent of ACTH stimulation. The pattern of response in man is similar to that previously reported in experiments on animals.

PLASMA METHIONINE AND METHIONINE UTILIZATION IN RELATION TO HEPATIC DAMAGE. *Harry E. Balch, George D. Michaels and Sadie Smyrl.* Inst. for Metabolic Research of the Highland Alameda County Hospital, Oakland, Calif.

In earlier reports from this laboratory it has been shown that patients with liver damage have significant impairment in their ability to remove administered methionine from the plasma. Further, those with severe liver damage had abnormal fasting levels for L-methionine. All of the original plasma methionine determinations were carried out by microbiologic assay procedures.

Using a simple chemical procedure developed in this laboratory (Michaels, 1953), plasma L-methionine has been determined in a group of normal individuals and in patients with liver damage. Using this technic, it appears that the fasting level of normal individuals is less than 0.5 mg./100 cc., as is the plasma level of individuals with liver damage of moderate degree. Those individuals with severe hepatic damage have higher fasting values. These values return to the normal level as the liver disease improves.

Many or most individuals with minimal liver damage have abnormal "methionine tolerance" following the intravenous infusion of L-methionine.

The technic is sufficiently simple to make the test feasible for use in the average clinical laboratory, and the sensitivity of the test appears to be such as to make it of significant value in evaluation of patients with known or suspected liver disease.

INFLUENCE OF 1,4,-DIMETHANE SULFONOXO BUTANE (GT-41) ("MYLERAN") UPON THE COURSE OF GRANULOCYTIC LEUKEMIA. *H. R. Bierman,* F. Cordes, K. H. Kelly, P. M. Aggeler* and M. Jacobs.* Div. Research, Hospital for Tumors and Allied Diseases, City of Hope Medical Center, Duarte, Calif., and the Dept. Medicine, Univ. California School of Medicine, San Francisco, Calif.

1,4-Dimethane sulfonyl butane has been shown by Timmis, Haddow and Galton to have a favorable effect upon patients with chronic myelogenous leukemia. In the original experience gained with this drug these investigators found that the effectiveness of GT-41 was limited to the chronic forms of granulocytic leukemia. This has been amply confirmed in the

two years' experience with this drug in this country. More recently, the effectiveness of GT-41 upon occasional cases with acute and subacute variants of granulocytic leukemia and a few cases of monocytic leukemia has been observed. The beneficial effects observed in these more fulminant forms of leukemia, united with the relative lack of toxicity with its cautious use, has encouraged its use in the more acute forms of granulocytic and monocytic leukemia.

The effects of GT-41 upon the bone marrow appear to be directed at the immature granulocytes and, in large doses, also at the megakaryocytes and platelet formation. The clinical benefits are characterized by decrease in hepatosplenomegaly and lymphadenopathy. A sense of well being occurs at or slightly before decrease in size of the spleen. The details of instituting and maintaining the patient with leukemia on this agent will be presented.

EVALUATION OF THERAPY IN SHOCK FOLLOWING MYOCARDIAL INFARCTION. *Maxwell J. Binder, James A. Ryan, Jr., Stanley Marcus, Frederick Mugler, Jr., David Strange and Clarence M. Aggress.** Medical Service, V. A. Hospital, and Dept. Medicine, School of Medicine, Univ. California, Los Angeles, Calif.

Lack of uniformity in the definition and classification of coronary shock in the literature is responsible for much of the variation in the reported incidence and mortality rates. Necessary clinical data for the formulation of criteria of severe coronary shock are defined. It is found desirable to report separately those patients whose shock responds to the administration of oxygen, relief of pain or correction of severe arrhythmias. Those patients in a terminal status or with complicating severe disease should also be reported separately.

An additional series of twenty-two patients treated non-specifically, and who fulfilled our criteria for severe coronary shock, is reported. The mortality rate of this group is 82 per cent. An additional series of fifty-one patients managed with modern therapy, and who fulfilled our criteria for severe coronary shock, is reported. The mortality rate of a group of sixteen patients treated with levarterenol is 75 per cent; that of a group of thirty-five patients treated with other vasopressor drugs or transfusion or both is 94 per cent. The most significant benefit with levarterenol is obtained in those patients who have complete heart block.

This study reveals that (1) there is need for uniform criteria for the classification of coronary shock and (2) treatment of coronary shock is still largely empirical. A small percentage of patients with this syndrome are probably benefited by the newer forms of therapy. However, the over-all failure to alter materially the mortality rate emphasizes the need for further elucidation of the mechanism of coronary shock.

REVERSIBILITY OF CHRONIC HEART FAILURE, INCLUDING TRICUSPID INSUFFICIENCY AND IMPAIRED LIVER FUNCTION FOLLOWING MITRAL COMMISSUROTOMY. *R. A. Bruce,* D. Donague and K. A. Merendino.* Univ. Washington, Seattle, Wash.

The importance of chronic venous hypertension and diminished cardiac output as primary factors in the mechanisms for both cardiac edema and vulnerability to hyponatremia, particularly postoperatively, was demonstrated in a patient who was submitted to surgery for mitral commissurotomy and cholecystectomy on separate occasions. Furthermore the ability to improve impaired liver function, as well as restore normal tolerance for exercise was demonstrated in the same patient also.

This patient was a thirty-two year old woman who was admitted for treatment because of unremitting and progressive orthopnea, dyspnea, cyanosis, abdominal enlargement and dependent edema of two and one-half years' duration. Physical findings and catheterization studies indicated severe mitral stenosis and tricuspid insufficiency with marked hypertrophy and dilatation of the right auricle and ventricle, auricular fibrillation, Class iv E. Mitral valve surgery was uncomplicated. Virtually all subjective symptoms disappeared. Cardiac murmurs became inaudible and the lungs cleared entirely. The liver receded in size and the expansile pulsations were no longer felt. Liver function improved, and plasma proteins increased to 8.2 gm. per cent. BSP retention declined to 0.8 mg. per cent. Cardiac catheterization revealed increased cardiac output, lower venous pressures, and confirmed the disappearance of tricuspid insufficiency. She had been greatly improved and clinically well for almost a year. Her physical activities are not restricted and there has been no recurrence of heart failure. The physical fitness index of exercise tolerance has increased from a preoperative value of 1.9

to 17.0 by six months after commissurotomy (normal range equals 13 to 26.)

ROLE OF CHYLOMICRA IN CHOLESTEROL TRANSPORT. *Sanford O. Byers* and Meyer Friedman.** Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif.

Knowledge of the physicochemical state in which cholesterol and fats are transported in body fluids is necessary to understand the metabolism of these substances and also for insight into the mechanism(s) of arteriosclerosis. Past work from this laboratory has shown that in the rat cholesterol is absorbed from the intestine entirely by way of the thoracic lymph. In the present study, samples of lymph and plasma from normal, nephrotic, bile duct obstructed, or Triton-treated rats, and from rats and rabbits on diets acutely or chronically high in cholesterol and fats, were obtained. These lymph and plasmas were centrifuged at 18,000 to 22,000 r.p.m. for one hour in the swinging bucket rotor of a Spinco preparative ultracentrifuge. This speed is sufficient to separate all turbidity as a fatty layer at the top but not great enough to bring about separation of lipoproteins in solution. The fatty top layer was then cut away from the clear lower layer in a liquid slicer, and the cholesterol, phospholipid and total fat content of the upper chylomicronous layer was compared with that of the clear lower layer. It was found that all the cholesterol absorbed into lymph is carried in particulate form as very finely divided chylomicra. These chylomicra undergo changes in number, size and composition after entering the blood stream; the changes may be of importance in determining whether or not hyperlipemia will develop. The possible significance of chylomicra in the hyperlipemic states of the various preparations will be discussed.

SOURCES OF ERROR IN THE DETERMINATION OF PLASMA VOLUME USING I¹³¹ LABELED HUMAN SERUM ALBUMIN (RIHSA) AND LIQUID GAMMA COUNTING. *Milton G. Crane and Ralph Adams.* Depts. Internal Medicine and Radiology, College of Medical Evangelists, Los Angeles, Calif.

A study has been made to determine the accuracy that may be expected in using RIHSA and liquid gamma counting in the determination of plasma volumes. This investigation revealed several possible sources of error in the method. The major ones are: (1) At this ex-

tremely low level of activity cross contamination from an intermediate or hot laboratory made the use of separate glassware necessary. (2) The use of RIHSA with a high free iodide content or the injection of material outside the vein will result in a falsely high calculated volume. (3) Variation of counting rates from duplicate standards averaged 1.0 per cent with a range from 0 to 2.9 per cent. This variation included pipetting errors, and slight differences in counting geometry. (4) Old standards (those prepared one or more days earlier) were inaccurate when compared with freshly prepared standards. (5) Standards prepared with plasma as a diluent produced more accurate counting rates than those prepared with water. (6) When counting whole blood, settling of the cells may lower the counting rate as much as 16 per cent. This effect is not important when employing the well-counter unless the sample more than half-fills the well. (7) The hematocrit may introduce errors in the following ways: (a) The amount of trapped plasma may vary from 2 to 8 per cent depending on the method. (b) Some anti-coagulants cause red blood cell shrinkage. (c) Marked variation in the peripheral hematocrit as compared to the total body hematocrit may be present in certain conditions.

Considering these possible sources of errors, the method is simple, accurate and reproducible.

CORRELATION OF QUALITATIVE AND QUANTITATIVE ESTIMATIONS OF NORMAL AND STRESS LYMPHOCYTES. *Jules A. Frank and Thomas F. Dougherty.** Dept. Anatomy, Univ. Utah College of Medicine, and V. A. Hospital, Salt Lake City, Utah.

Surface area measurements of blood lymphocytes and lymphocyte nuclei from humans and experimental animals were made. Frequency distributions of the various sizes of lymphocytes were determined. These data were compared with lymphocyte counts from the same material using morphologic criteria alone (i.e., small, "normal" lymphocytes and large, "stress" lymphocytes).

Statistical analyses of cell and nuclear sizes of lymphocytes from normal subjects resulted in smooth frequency distribution curves representing significantly larger lymphocytes. Lymphocytes of intact mice were found to be smaller than those of stressed, adrenalectomized mice. Absolute numbers of normal and stress lymphocytes determined by morphologic criteria cor-

related with absolute numbers of small lymphocytes and large lymphocytes, respectively, determined by actual measurement.

Since it is well documented that the "infectious mononucleosis" lymphocytes are not pathognomonic for that disease but occur normally and in a host of other disease entities, it becomes possible to determine whether the lymphocyte size distribution curve of a given patient is within the normal range. An example of the larger lymphocyte population of an untreated Addisonian reverting to the normal range following hydrocortisone treatment will be discussed as well as other clinical entities.

EFFECT OF CORTISONE UPON THE HYPOTENSION AND DIMINISHED PERIPHERAL VASCULAR REACTIVITY OF POTASSIUM-DEFICIENT RATS. *S. Charles Freed, Ray H. Rosenman* and Malcolm Smith.* Harold Brunn Institute, Mount Zion Hospital, San Francisco, Calif.

Repeated studies from this laboratory have shown that prolonged restriction of dietary potassium induces a depressor effect, both in intact and renal hypertensive rats. The hypotensive response to potassium deprivation was found to be associated with a diminished peripheral vascular responsiveness to pressor substances.

Recently we have found that administration of cortisone acetate rapidly restores these lowered blood pressures to their initially normotensive or hypertensive levels, respectively, without correcting the potassium-depletion of the tissues or blood. This response is in marked contrast to the effect of desoxycorticosterone acetate under similar conditions. Thus DCA was found to exert a further lowering of the blood pressure in intact and renal hypertensive rats that were depleted of potassium.

The administration of cortisone to hypotensive, potassium-deficient rats has been found to induce restoration to normal of the peripheral vascular responsiveness to nor-epinephrine and methoxamine. It is suggested that the pressor effect of cortisone in such rats may be at least partly due to this concomitant restoration of vascular sensitivity to pressor substances. However, the mechanism of the pressor effect of cortisone in such rats has not been clarified. Current studies are being directed at determining whether the ability of cortisone to correct the circulatory abnormalities is indicative of an absolute or relative deficiency of adrenocortical

steroid secretion induced by prolonged potassium depletion.

CHANGES IN BLOOD 17-HYDROXYCORTICOSTEROIDS AND LEUKOCYTES FOLLOWING ACUTE WHOLE BODY X-IRRADIATION IN THE RHESUS MONKEY. *Arthur B. French, Claude J. Migeon, Leo T. Samuels* and John Z. Bowers.* Gastrointestinal Div., Radiobiology Laboratory, Depts. Biological Chemistry and Medicine, Univ. Utah College of Medicine, Salt Lake City, Utah.

Plasma 17-hydroxycorticosteroid levels and blood eosinophil counts were followed in twenty-two Rhesus monkeys after acute whole body irradiation. Other hematologic studies are also included to correlate the timing of these changes with the classic manifestations of radiation injury. Plasma corticosteroid values in normal monkeys show a daily cycle with an average high point of 56 $\mu\text{g.}/100\text{ ml.}$ at 6 A.M. This falls sharply to 39 $\mu\text{g.}/100\text{ ml.}$ by 9:00 A.M. and 29 $\mu\text{g.}/100\text{ ml.}$ by noon, and then decreases slowly until a rise begins at midnight. Eosinophil levels show a reciprocal cycle while polymorphonuclear leukocyte levels have a parallel cycle. After irradiation with 800 r there is a rapid rise in steroid levels, reaching a peak averaging 87 $\mu\text{g.}/100\text{ ml.}$ at four to six hours. At twelve hours the levels are normal and remain so until a second rise a few days before death. This late rise reaches levels higher than those caused by ACTH stimulation and a different mechanism is suggested. Leukocyte levels show related stress effects which are modified later by radiation damage to bone marrow. The steroid changes are maximal with 400 r, but do not occur with 100 r or less. With doses of 50 r or higher there is a sharp drop in eosinophils. Survival time after 800 r is directly proportional to body size.

METABOLISM OF RAT SKIN FOLLOWING EXPOSURE TO LOW TEMPERATURES. *Frederick A. Fuhrman.* Dept. Physiology, Stanford Univ. School of Medicine, Stanford, Calif.

Two mechanisms have been proposed to explain the tissue damage produced by cold injury of the type in which actual freezing occurs (frostbite). Either the injury is the direct result of ice formation or the cellular injury is the secondary result of reduced blood supply following thawing. Investigation of the effects of exposure to low temperatures on oxygen consumption of rat skin have been carried out in order to provide fundamental information which might aid in deciding between the two mechanisms. Skin

from the dorsal surface of the rat foot gave reproducible rates of oxygen consumption which were constant for three hours at 37.5°C. The QO_2 of a skin sample was measured at 37.5°C., the sample was cooled as desired, and the QO_2 of the same sample was again determined at 37.5°C. Low final rates of oxygen consumption are an indication of tissue damage resulting from cooling. Exposure in this way to temperatures from +1°C. to -4°C. for one to twenty-two hours did not result in tissue damage. Exposure to -25°C. for one hour, during which freezing occurred at least in the fluid medium resulted in a final QO_2 of 23 per cent of the initial. After exposure for one hour at -10°C., at which freezing does not uniformly occur in all samples, frozen samples had a QO_2 about 10 per cent lower than that of unfrozen samples exposed under the same conditions.

HEMODYNAMIC AND WATER-ELECTROLYTE RESPONSE IN DOGS TREATED WITH DIPHTHERIA TOXIN. *H. E. Griswold, Jr. and W. W. Hurst.** Depts. Physiology and Medicine, Univ. Oregon Medical School, Portland, Ore.

Hemodynamic responses were observed in nine dogs, each anesthetized with morphine-Na barbital. Cardiac outputs were determined by direct Fick at forty-five minute intervals for three determinations to obtain baseline values. Four to ten days later diphtheria toxin was administered intravenously in dosage arbitrarily chosen previously to produce marked illness or death in three weeks' time. Ten to twelve days after injection outputs were again obtained under the same conditions and anesthesia as in the control studies. Cardiac output and stroke volume was unchanged in three and fell significantly in six. Mean arterial pressure, right atrial pressure and oxygen consumption showed inconsistent changes.

Endogenous creatinine clearance was determined in five animals under the above conditions. Filtration rate fell in all, the change averaging from 46 to 14.4 cc./min. (range 54.1 down to 3.0 cc./min., and 41.5 to 26.5 cc./min.)

Gluteal muscle biopsies, blood electrolytes, T-1824, thiocyanate, D_2O volumes and body weights were determined in seven dogs as above except that the dosage of toxin was reduced to prevent complicating affects of vomiting and diarrhea. Total muscle water remained relatively unchanged, while extracellular muscle water uniformly fell and intracellular muscle water uniformly rose. The average fall was 44

cc./kg. fat free muscle (+13 to -105 cc./kg.), and the average rise was 47 cc./kg. fat free muscle (-14 to +90 cc./kg.), respectively. Intracellular sodium and potassium changes in concentration were inconsistent. Correlated with these changes was a consistent fall in plasma volume (in all but one) and in thiocyanate space. Total body water tended to rise slightly and body weight fell an average of 0.2 kg.

The observed responses consisted of a tendency for cardiac output and stroke volume to fall, reduction of glomerular filtration rate, reduction of extracellular fluid volume, and increase of intracellular muscle water with little change in total body water or weight.

MUSHROOM POISONING. TWO CASES CAUSED BY A PREVIOUSLY UNIDENTIFIED SPECIES, ONE WITH SEVERE GASTROINTESTINAL, LIVER, RENAL AND BRAIN DAMAGE. *Charles M. Grossman* and Barney Malbin.* Portland, Ore.

Two patients who ate wild mushrooms became severely ill after a ten-hour latent period. The wife vomited a considerable amount of undigested mushrooms and was much less ill, recovering from a severe gastroenteritis in two weeks. The husband was desperately ill with hemorrhagic gastroenteritis, acute adynamic ileus, renal failure, severe and prolonged hepatic damage, hemorrhagic meningo-encephalitis and acute pulmonary edema. Recovery was followed by prolonged convalescence with a positive cephalin flocculation test persisting three months after onset.

The mushroom was identified as belonging to the genus *Galerina* and named *Galerina venenata* Smith (Mycologia, in press). No case of poisoning by this species had been previously known or reported.

Recent work describing the isolation and chemical identification of some mushroom poisons will be briefly reviewed.

AN HYPOTHESIS CONCERNING THE RELATION OF LIFE STRESS TO THE NATURAL HISTORY OF TUBERCULOSIS. *Thomas H. Holmes.** Seattle, Wash.

Ecologic and psychosocial studies in approximately 1,000 patients with tuberculosis have revealed that a background of social deviancy, emotional insecurity and unrealistic striving have contributed to emerging patterns of social isolation and personality disintegration culminating with the discovery of tuberculosis. The circumstances surrounding the onset of

the disease were those of continued or increasing life stress acting on individuals whose limited capacities for adjustment were no longer adequate for resolving problems or achieving satisfaction. The way such stress may influence the natural history of tuberculosis has been studied. The urinary excretion of 17-ketosteroids utilized as an index of adrenocortical function, has been correlated with behavior and pulmonary tuberculosis in 109 hospitalized patients. The mean 17-ketosteroid value in twenty-five females (fifty determinations) was 8.61 mg./24 hours with a range of 2.38 to 24.70 mg./24 hours. In eighty-four males (200 determinations) the mean was 8.93 mg./24 hours with a range of 1.78 to 38.42 mg./24 hours.

Fibrotic disease, usually limited in extent, was characteristically found in tense, anxious, restless patients who were neither acutely ill nor febrile but whose interpersonal and social adjustments were conflict-ridden. In these patients the 17-ketosteroid levels were 20 mg./24 hours or over. Conversely, exudative disease, usually of considerable extent, characteristically occurred in acutely ill, febrile patients who were also withdrawn, apathetic or depressed. In these patients the excretion of 17-ketosteroids was 2 mg./24 hours or less. The 17-ketosteroid values for these two categories of patients differed statistically.

During the study, spread of disease occurred only when patients were clinically depressed and 17-ketosteroids were low. However, low 17-ketosteroids and depression were not invariably associated with spread. Improvement in disease was closely related to achievement of a comfortable adjustment and return of 17-ketosteroid values to normal range.

From these data it is inferred: (1) that adrenocortical hormones play a role in the mechanisms of resistance in tuberculosis; and (2) that life stress, by engendering alterations in pituitary adrenocortical function, may influence resistance to the disease.

COMBINATIONS OF RAUWOLFIA AND AMPHETAMINE. *Norman W. Karr* and George E. Cronheim.* Los Angeles, Calif.

Rauwolfia serpentina has been used in this country principally for its hypotensive activity. This is only one of the three major actions of the drug: sedation, bradycardia and hypotension. At clinical doses, the sedation is mild and usually without somnolence, and is perhaps best described as a "tranquilization," associated with

a sense of well being. At these doses, hypotension and bradycardia are not apparent when blood pressure and pulse rate have previously been normal.

Because of these properties, a combination of amphetamine and Rauwolfia would appear to offer some promise for mood elevation in those vague anxieties, tensions and depressions. If such a combination is to have practical value it must produce neither excessive sedation nor excessive stimulation but must manifest the mood-elevating properties of both Rauwolfia and amphetamine. This paper presents animal and human data that such a combination of virtues is possible and practical.

Mice have been tested in "jiggle cages" where they manifest decreased activity after an alkaloidal extract of Rauwolfia, and increased activity after amphetamine. It has proved possible to balance these two effects so that neither is apparent after appropriate doses of the two drugs. Humans have shown good "mood-elevation" from a combination of 1 mg. of Rauwolfia alkaloids and 5 mg. of dl-amphetamine, without manifesting either depression or undesirable stimulation. Measurements of the effects of the agents separately and together on human tremor are in progress and will be reported.

ADRENAL STEROID EFFECTS UPON EXPERIMENTAL NEPHRITIS. DEPENDENCE UPON ROUTE OF ADMINISTRATION. *Richard W. Lippman* and Dan H. Campbell.** Gates and Crellin Laboratories of Chemistry, California Inst. of Technology, Pasadena, Calif.

Experimental nephritis was produced in the rat by administration of rabbit anti-rat kidney gamma globulin (NTG). Adult male rats of the Slonaker-Addis strain were given a single, constant, intravenous dose of NTG, followed by daily administration of cortisone or DCA for four weeks. The stock diet contained 17 per cent protein and 0.48 per cent NaCl.

Subcutaneous cortisone increased proteinuria and blood pressure elevation. In contrast, intraperitoneal cortisone failed to affect proteinuria or blood pressure elevation. It is believed that the difference represented the net effect of (1) slow, continued absorption from subcutaneous sites; (2) rapid absorption from the peritoneal cavity; (3) rapid disappearance from the circulation. The results are consistent with physiologic differences related to the route of administration by Greenspan, Gifford and Deming.

Subcutaneous DCA increased blood pressure elevation but had little effect on proteinuria. Intraperitoneal DCA resembled subcutaneous cortisone and increased both the proteinuria and the blood pressure elevation. It is suggested that, in the case of DCA, the difference resulted from the hepatic passage of intraperitoneal DCA, with formation of metabolic products of altered activity.

EFFECT OF STEROID ADMINISTRATION ON INFERTILE OVARIAN DEFICIENCY CYCLES. *Robert A. Lyon.** Inst. of Experimental Biology, Berkeley, Calif.

Everett's demonstration of reversion of constant estrus cycles in the rat prompted steroid administration to forty-six infertile women with cyclic irregularity but no other demonstrable infertility factors. Ovarian failure criteria from basal temperature data were employed, the endpoint being reversion toward normal cyclic patterns and the establishment of pregnancy. The control cycle characteristics are contrasted with the steroid treatment cycles. The mean control cycle length was thirty days (25-42) and the progestational phase was 13.6 days (12-16) while the mean apparent ovulation day was 16.3 (12-29). When a steroid was administered during a preconceptional cycle a change in the pattern toward normal ensued. Mechanical (cervical or tubal) infertility norms served as pattern controls.

Abnormal ovarian cycles attributable to persistently excessive hormone influence such as granulosa cell tumor or long-continued estrin administration were not found in this group. The present study cycles were, however, associated with signs of ovarian deficiency.

The following table summarizes cycle changes of steroid-treated ovarian fertility at conception:

Steroid	No. Patients	Dose mg. Daily	Administered Cycle Day
Progesterone intramuscularly	11	10	12-14
Anhydrohydroxy-progesterone orally . . .	14 9	30-60 30	12-14 prior cycle
Ethinyl estradiol orally . .	12	.02	prior cycle

When the material is regrouped as to those receiving the steroid during the conceptional cycle and those receiving it during the immediate preconceptual cycle, it appears that the cycle characteristics are influenced by the steroid.

DIAGNOSIS OF "TIGHT" TRICUSPID STENOSIS.
Malcolm C. McCord and S. Gilbert Blount, Jr. Univ. Colorado School of Medicine, Denver, Colo.

Simultaneous surgical correction of tricuspid and mitral valve stenosis was attempted in three patients. Stenosis of both valves was present in one patient and was partially relieved by digital valvuloplasty. In two patients there was significant mitral stenosis but the tricuspid valve was only moderately stenotic and was not amenable to surgical correction.

The preoperative studies were therefore evaluated in an attempt to determine criteria for the diagnosis of surgical tricuspid stenosis. The clinical findings revealed no distinguishing elements. Cardiac catheterization revealed a low, fixed, cardiac index, an increased A-V oxygen difference, and an elevated pulmonary artery and pulmonary "capillary" pressure in all patients. The right atrial pressure was considerably elevated in all patients with a pressure wave during ventricular systole indicating tricuspid insufficiency. High presystolic pressure waves were present in the two patients with non-surgical valves, there being a sinus rhythm.

In the patient with surgical tricuspid stenosis there was a wide pressure gradient from the right atrium, 14 mm. Hg to the right ventricle, 5 mm. Hg, during early diastole. This gradient increased from 9 mm. Hg at rest to 17 mm. Hg following exercise. A reduction of this pressure difference to 3 mm. Hg occurred following surgery. In the two patients with non-surgical tricuspid valves only a small gradient of 2 mm. Hg and 3 mm. Hg was present.

It was concluded that a significant pressure differential between the right atrium and right ventricle in early diastole was a diagnostic feature of "tight" tricuspid stenosis.

BLOOD (RED CELL) VOLUME MEASURED BY CARBON MONOXIDE AND RADIOCHROMIUM METHODS. *Norman Nomof, James Hopper, Jr.,* Reidar Wennesland, Kenneth G. Scott and Ellen Brown.** Dept. Medicine and the Radioactivity Center, Univ. California School of Medicine, San Francisco, Calif.

JULY, 1954

CO and Cr₅₁-available spaces were determined simultaneously under resting conditions in six healthy subjects and twenty-nine patients with various diseases. In all but two of the thirty-five subjects the CO space was greater than the Cr₅₁ space, and the average discrepancy was 16 per cent. The difference in spaces was of the same magnitude in disease states as in health. Distribution of both CO and Cr₅₁-tagged cells was complete within twenty minutes, and Cr₅₁ space remained nearly constant for twenty-four hours. It was concluded that (1) the entire contents of the vascular compartment are reached by these indicators and (2) CO is distributed to a space which is about 16 per cent larger than intravascular red cell volume.

ADVANTAGES AND LIMITATIONS OF CULDOSCOPY.
Robert W. Noyes. San Francisco, Calif.

A pelvic endoscopic technic, popularized and named culdoscopy by Albert Decker, has been enthusiastically reported in the literature. On the Stanford Gynecology service, culdoscopy has been used in the diagnostic problem type of case. In a recent four-year period 130 culdoscopies have been done by thirteen operators. Of these, twenty-one (16 per cent) were failures, fifty-six (43 per cent) were successful and fifty-three (41 per cent) were partially successful. In thirty-six patients the indication for culdoscopy was ectopic pregnancy, and an apparently correct diagnosis was made in twenty-five of these. In twenty-eight patients the clinical diagnosis was pelvic inflammatory disease, in twenty-six it was endometriosis and in twenty-six pelvic mass. A correct diagnosis was apparently established in twenty-two, twenty-three and nineteen of these, respectively. Less than one-third of the patients were operated upon, indicating a high level of confidence in the culdoscopic findings. Significant diagnostic error was noted in 4.5 per cent of patients who were subsequently operated upon. When symptoms are out of proportion to physical, laboratory and x-ray findings, and when there is a need for conclusive diagnosis, which only direct visualization can give, culdoscopy is safer, cheaper and less disabling than laparotomy. Culdoscopy is at its best when there is little or no pelvic disease, yet when the cause of infertility or of obscure pelvic pain remains unsolved by the usual diagnostic methods. Culdoscopy is not very successful in the diagnosis of painless pelvic masses. Culdoscopy has not supplanted, nor even directly competed with

exploratory laparotomy on our service. Rather it has supplemented operative technics by selecting proper candidates for surgery.

MEASUREMENT OF PORTAL VENOUS PRESSURE BY HEPATIC VEIN CATHETERIZATION. *Telfer B. Reynolds, Donald C. Balfour, Jr., David C. Levinson, Oscar Magidson, William P. Mikkelsen and Arthur C. Pattison.* Depts. Medicine and Surgery, Univ. Southern California School of Medicine and the Los Angeles County Hospital, Los Angeles, Calif.

In an effort to measure portal venous pressure a cardiac catheter was passed through the right auricle and inferior vena cava and wedged into a peripheral hepatic vein. In thirty-four patients with cirrhosis the pressure in this position was elevated (mean 21 mm. Hg above right auricle) and fell abruptly (to a mean of 8 mm. Hg above right auricle) as the catheter was withdrawn to a free position in the hepatic vein. This abrupt gradient was not seen in patients without cirrhosis.

Comparisons of wedged hepatic vein pressure (W.H.V.P.) and portal vein pressure (P.V.P.) were made in twelve cases with portal hypertension. In six patients at surgery W.H.V.P. varied from 4 to 24 per cent (mean 18 per cent) lower than simultaneously recorded P.V.P. In two postoperative patients W.H.V.P. was 8 and 4 per cent lower than P.V.P. recorded simultaneously from a polyethylene tube previously placed in the portal system. In four patients W.H.V.P. measured immediately preoperatively varied from 10 to 21 per cent (mean 16 per cent) lower than P.V.P. measured at surgery. W.H.V.P. is thus considered to provide a reliable indirect estimate of P.V.P.

In five patients treated by hepatic arterial ligation W.H.V.P., measured four to eighteen months postoperatively, averaged only 11 per cent lower than P.V.P. previously recorded at surgery, suggesting failure of the operation to lower portal hypertension.

W.H.V.P. has proven of great value in assessing the need for portacaval surgery in patients with cirrhosis and gastrointestinal bleeding.

HISTOCHEMICAL STUDIES OF THE HYALINE ISLETS OF DIABETES. *J. F. Rinehart, W. E. Toreson and S. K. Abul-Haj.* Dept. Pathology, Univ. California School of Medicine, San Francisco, Calif.

While hyaline alteration of the islets of Langerhans is found in approximately 40 per

cent of cases of diabetes, the nature of the hyaline material is not understood. Using a colloidal iron staining technic previously described (Rinehart and Abul-Haj), the material reacts in the manner of an acid mucopolysaccharide. In the early phases the mucinous material is found to lie at the periphery of the delicate capillaries of the islets. Increasing accumulation of this substance eventually obliterates the cells of the islet. The derivation of the hyaline mucoid material is not known although it would appear to be derived from the endothelium rather than the epithelium. It is pointed out that even minor accumulations of such material might constitute a significant barrier to the release of insulin.

SPERM MOTILITY—A SIMPLE METHOD FOR ANALYSIS. *Roberta Schwartz and Hans Zinsler.** Dept. Surgery, Univ. Southern California Medical School, Los Angeles, Calif.

The capacity of undiluted sperm to migrate upward in a capillary tube into Ringer's solution has been standardized in proven fertile and infertile mild donors, carrying out observation with oil immersion over a period of two hours. Specimens showing 25 to 66 per cent motility showed upward progression averaging 5 mm. Specimens under 25 per cent motility showed downward progression of 2.2 mm. The standard deviation of duplicate samples is 1.7 mm. and of successive samples, 1.5 mm. Correlations with refrigeration, period of continence, total count and live:dead ratio have been analyzed, and the method adapted for studies with surgical mucus and contraceptives.

BIOASSAY OF MELANOCYTE STIMULATING SUBSTANCE IN HUMAN URINE. *Kazuo Shizume and Aaron Bunsen Lerner.* Div. Dermatology, Univ. Oregon Medical School, Portland, Ore.

A bioassay method for quantitative determination of the melanocyte-stimulating hormone (MSH) has been devised. This method utilizes changes in light reflection from isolated frog skin before and after immersion in solutions containing MSH. A photoelectric reflection meter is used for the measurements. Within certain limits, the logarithm of MSH concentration is proportional to the ratio of the changes in reflectance obtained with unknown and standard amounts of hormone.

The melanocyte-stimulating substance in the urine is absorbed onto fine particles of benzoic acid. The latter are then dissolved in acetone,

leaving the melanocyte-stimulating substance in the precipitate. The active substance is extracted with 80 per cent ethanol, and the extract is assayed by reflectance measurements. Application of this method to twenty-four-hour urine specimens from 110 patients yielded the following preliminary results: (1) Most of the normal males and females excreted very small but detectable amounts of melanocyte-stimulating substance. (2) Most of the pregnant women had an increased output of melanocyte-stimulating substance. (3) Many patients with Addison's disease showed a high urinary output of melanocyte-stimulating substance. (4) Some patients with pigmentary disorders excreted increased amounts of melanocyte-stimulating substance.

The relationship of these results to the pigmentation of Addison's disease and other conditions will be discussed.

INHIBITION OF PANCREATIC JUICE ENZYMES BY DFP (Di-Isopropyl Fluorophosphate). *John Ward and B. V. Jager.** Salt Lake City, Utah.

Several observers have reported the inhibitory effect of DFP upon isolated preparations of

trypsin and chymotrypsin. In the study to be considered here, samples of dog pancreatic juice were incubated *in vitro* with varying concentrations of DFP and with varying hydrogen ion concentrations. Pancreatic amylase, lipase and protease showed differing susceptibility to inhibition by DFP. No pancreatic enzyme was inhibited by quantities of DFP which were not 100 to 1,000 times greater than the amount needed *in vitro* to inhibit erythrocyte cholinesterase. Further it could be demonstrated that enterokinase, needed for conversion of trypsinogen to trypsin, is inhibited by DFP.

A permanent pancreatic fistula was produced in a dog. Repetitive doses of DFP administered parenterally to this animal failed to inhibit any pancreatic enzyme although complete inactivation of serum and erythrocyte cholinesterase was achieved. Under investigation is the effect of DFP upon pancreatic enzymes when this agent is introduced directly into the abdominal aorta. The findings in this experiment will be reported.

The ultimate intent of this investigation is to determine whether or not DFP may be useful in the treatment of patients with acute pancreatitis or with pancreatic fistula.

Case Reports

Physiologic Studies in a Patient with a Pulmonary Arteriovenous Fistula*

HERBERT N. HULTGREN, M.D. and FRANK GERBODE, M.D.
San Francisco, California

SINCE the initial description of a case of pulmonary arteriovenous fistula in 1917 by Wilkens,¹ the re-emphasis of this lesion as a cause of chronic cyanosis in 1938 by Rodes,² and the first successful surgical extirpation of the lesion in 1942 by Hepburn and Dauphinee³ many cases have been reported and several excellent studies of the clinical, radiologic and physiologic features of this interesting disease have been made.⁴⁻¹² It is apparent that such pulmonary arteriovenous communications are more common than originally believed, that they can be diagnosed by ordinary clinical methods and, in the majority of cases, a complete cure by surgery can be accomplished.

The typical patient, commonly between twenty and thirty years of age, usually gives a history of chronic cyanosis appearing or becoming more intense late in childhood. Severe physical incapacity such as is common in cyanotic congenital heart disease is not present. Hemorrhages from the nose or gastrointestinal tract and hemoptysis may have occurred. A family history of polycythemia, hemorrhages or "blood blisters" on the skin may be obtained. Occasionally, neurologic symptoms and epilepsy due to intracranial hemangiomas may be present.

The essential physical findings consist of cyanosis and clubbing of the digits in the presence of a normal heart. In about a third of the cases extracardiac murmurs may be found at various places over the chest, usually over the lower portions. The murmurs may be continuous but may occasionally occur only in systole or diastole. A Valsalva maneuver may obliterate or alter their intensity. The finding of minute to olive-sized blue-black hemangiomas in the skin or on the lips and buccal mucosa is of

importance since they may be the external manifestations of a systemic vascular dysplasia of which the pulmonary lesions are physiologically the most important. The packed cell volume may be as high as 90 per cent and the hemoglobin and number of red blood cells are similarly increased. The electrocardiogram shows no evidence of right ventricular hypertrophy and may be normal or demonstrate only minor abnormalities in the T waves or axis deviation. In most cases confirmation of the clinical diagnosis is possible by finding in the roentgenograms of the lung a vascular shadow connected to the hilum by strand-like densities. Although usually present in the lower lobes, in about 30 per cent of cases the lesion may be adjacent to the hilum and planigraphy or demonstration of alteration in size of the mass by the Valsalva maneuver (decrease in size) or Mueller maneuver (increase in size) may be necessary. Angiocardiography probably should be done in all cases, however, to outline the fistula accurately and to demonstrate smaller communications not visible in conventional films.

These patients are frequently erroneously diagnosed as cases of cyanotic congenital heart disease or polycythemia vera. The absence of murmurs, normal electrocardiogram and normal cardiac silhouette by x-ray usually is sufficient to rule out the former possibility. When available, cardiac catheterization is of value in excluding a congenital cardiac lesion. Detection of a low oxygen saturation in the arterial blood will rule out polycythemia vera. It is quite possible that determination of the arterial oxygen saturation in all cases diagnosed as polycythemia vera would detect an occasional instance of pulmonary arteriovenous fistula, especially in those cases without the increase

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in leukocytes, platelets and immature cells that are characteristic of Vaquez-Osler's disease.

The pulmonary lesion consists of single or multiple bluish vascular masses located usually subpleurally in the lower lobe and connecting, by cavernous blood-filled spaces, large branches of the pulmonary artery and pulmonary vein. The structure is that of a cavernous hemangioma with many dysplastic vascular elements in the wall. Calcification or rupture with hemorrhage may occur. The communication may enlarge slowly with increasing age.

The physiologic features of pulmonary arteriovenous fistula have been investigated by the technic of cardiac catheterization in seven cases.⁹⁻¹² The arterial unsaturation is due to pulmonary artery blood being shunted through the fistula into the pulmonary vein without being oxygenated by passage through the capillary bed of the lung. As much as 70 per cent of the entire cardiac output may thus by-pass the pulmonary alveoli. Despite the magnitude of the shunt the pulmonary artery pressure is normal and the cardiac output is only occasionally increased. These features, in contrast to the systemic arteriovenous fistula in which a high cardiac output and cardiac overwork are common, are probably related to two factors: (1) The low pressure and great distensibility of the pulmonary vascular bed and (2) the small pressure gradient between the pulmonary artery and pulmonary vein present across the fistula. Calculations of the vascular resistance of the lung exclusive of the fistula have shown it to be approximately double that of a normal lung. The cause of this is not known. No studies of the circulation during exercise have been made in this disease except that of Maier and his group⁹ who noted a fall of the arterial oxygen saturation.

Because it was possible to study a typical case of pulmonary arteriovenous fistula by cardiac catheterization under conditions of rest and exercise both before and after successful extirpation of the lesion, this report is presented.

METHODS

Cardiac catheterization was performed as described by Cournand.¹³ Blood pressures were measured by means of a Hamilton manometer. Blood gas analyses were performed in duplicate in a Van Slyke apparatus. Expired air was collected in a Tissot apparatus and duplicate gas analyses were made in a Henderson-Haldane apparatus. Exercise was accompanied in the

supine position by pushing against a hinged, counterweighted footboard. Five minutes of exercise was performed and expired air was collected for the final three minutes. Duplicate blood samples were drawn at the middle of the gas collection period. Intracardiac pressures are referred to the mid-point of the chest. Vascular resistances were calculated and corrected for blood viscosity using the following formula as described by Friedlich.¹¹ Resistance (mm. Hg/L./min./M²) =

$$\frac{\text{mean pressure fall (mm. Hg)}}{\text{blood flow (L./min./M}^2\text{)}}$$

corrected for blood viscosity. Since the left auricular pressure was not known, the mean pulmonary artery pressure was used as the numerator. The calculation of separate resistances was attempted merely to evaluate, in a very crude fashion, the degree of obstruction to blood flow produced by the lung and fistula separately and to compare our data with similar data obtained in other cases. The value thus derived may be more accurate than grading the vascular resistance from one to four plus but it certainly is not as precise as the suffix, "dynes/m⁵/sec.," implies. We agree with the comments of Burton¹⁴ concerning the deceptions implicit in formulas built upon unstable assumptions.

Blood volume was measured by Evans blue dye as described by Noble and Gregersen.¹⁵ Samples were collected from the femoral artery before the injection of dye and at ten, twenty and thirty minutes afterward to exclude the possibility of delayed mixing of dye causing an error in the calculations. Platelet counts were made in duplicate by the direct method, using the Rees-Ecker diluting fluid, and counts were checked by two observers.

CASE REPORT

This twenty-three year old white American dishwasher entered the Stanford Hospital for the first time December 9, 1951, complaining of cyanosis and exertional dyspnea since childhood. He was noted to be cyanotic at birth. He was distinctly retarded mentally, not being able to walk until three and one-half years of age, entering the first grade at twelve years and finishing the sixth grade with much difficulty. After a fall from a table at two years he had had occasional convulsive seizures until he was five.

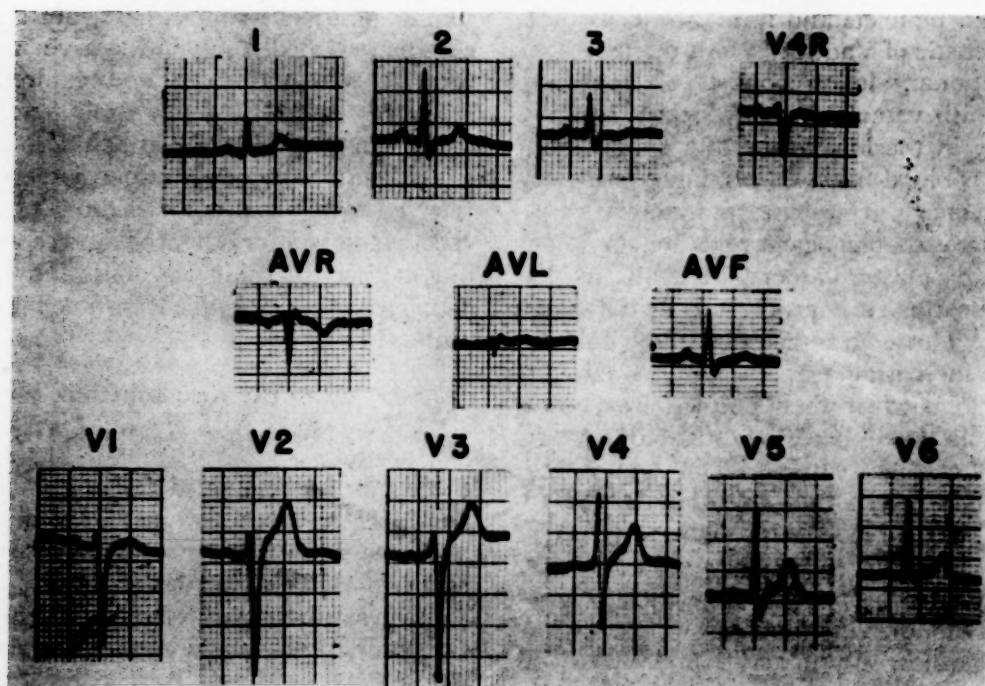


FIG. 1.



FIG. 2. Preoperative anteroposterior roentgenogram of chest of patient described in this paper.

At twelve he was hospitalized because of a staggering gait and poor speech and x-rays revealed a deformity of the posterior portion of the right lateral ventricle. After a bout of pneumonia at thirteen he noted increasing cyanosis, especially in cold weather, and dyspnea and weakness of his legs on exertion. At the time of his hospital entry he could walk a mile

slowly on the level, climb two flights of stairs and perform his job as a dishwasher with moderate dyspnea. He occasionally had noted blood-streaked sputum and nosebleeds especially during upper respiratory infections. There was no history of squatting. His father, mother and an older sister and brother were alive and well. Their chest films were normal and none of them were cyanotic. Two months before entering the hospital a hemangioma had been removed from above the right ear so that his hat would fit properly.

Physical examination revealed a large, mentally retarded male with marked cyanosis of the mucous membranes. A few small hemangiomas were present over the upper anterior chest. There was marked clubbing of fingers and toes. The chest was clear and no cardiac murmurs were heard. The blood pressure was 105/65 mm. Hg.

Laboratory studies revealed a red blood cell count of 8.7 million per cu. mm.; hemoglobin, 26.5 gm.; packed cell volume, 83 per cent with an MCV of 93, MCH 31 and MCHC 30. The total white blood count was 7,000 per cu. mm. with a normal differential count. There were 50,000 platelets per cu. mm. The bleeding time was six and one-half minutes. The retractile power of the clot was poor. There were 1.2 per cent reticulocytes. A smear of aspirated bone marrow revealed erythroblastic hyperplasia and normal megakaryocytes. A urinalysis was

negative. The Kahn test was negative. The blood urea was 12 mg. per cent. The arm to tongue circulation time using 5 cc. of decholin® was twenty-seven seconds. An electrocardiogram (Fig. 1) was normal. X-rays of the chest (Fig. 2) revealed a prominent, rounded density in the

rib bed. The fistula presented on the surface of the left lower lobe, pulsated moderately, and eddy currents could be seen in its thin wall. The pulmonary artery supplying the fistula was dilated and thin, as was the inferior pulmonary vein. No other vascular anomalies were noted in

TABLE I
RESULTS OF STUDIES PERFORMED BEFORE AND AFTER COMPLETE SURGICAL REMOVAL OF A PULMONARY ARTERIOVENOUS FISTULA

	Preoperative		Postoperative	
	Rest	Exercise	Rest	Exercise
Pulmonary ventilation, L./min.	13.3	18.3	9.6	15.9
Oxygen consumption, cc./min.	347	522	285	561
Brachial artery oxygen content, cc./100 cc.	27.4	28.0	19.5	20.1
Arterial O ₂ saturation %	80	82	90	92
Right ventricle oxygen content, cc./100 cc.	22.9	20.8	15.9	14.2
Peripheral AV difference, cc./100 cc.	4.5	7.2	3.6	5.9
Cardiac output, L./min.	7.7	7.3	7.9	9.5
Effective pulmonary blood flow, L./min.	3.6	4.5	7.9	9.5
Flow through shunt, L./min.	4.1	2.8	0	0
Right ventricle pressure, mm. Hg.	22/4	24/2	15/5	16/3
PA pressure—mean mm. Hg.	16	18	10	11
Brachial artery pressure, mm. Hg.	120/83	121/92
Total pulmonary vascular resistance, mm. Hg./L./min./M ² .	4.1	4.6	4.0	4.8
Resistance of shunt, mm. Hg./L./min./M ² .	7.7	12
Resistance of vascular bed, exclusive of shunt.	8.8	7.5
Packed cell volume %	83	47
Hemoglobin, gm./100 cc.	26.5	15.8
Whole blood volume, cc.	9120	5760
Plasma volume, cc.	2520	3430
Red blood cell volume, cc.	6600	2330
Platelet count per cu. mm.	50,000	132,000
Bleeding time, minutes	6½	2½
Clot retraction	Poor	Normal

left lower lung field just above the diaphragm. Several vessels were seen running from the mass to the left hilum. The mass did not pulsate nor did it visibly change in size during the Valsalva or Mueller maneuvers. It was readily opacified after the rapid intravenous injection of 40 cc. of 75 per cent neoipax.® Cardiac catheterization studies were performed with the results summarized in Table I. No intracardiac shunts were demonstrated, as evidenced by the minimal difference in oxygen contents of the following samples expressed in cc. per 100 cc. of blood: inferior vena cava 24.0, superior vena cava 20.9, right auricle 23.8, right ventricle 22.9, pulmonary artery 23.0, coronary sinus 12.2.

On December 12, 1951, a left lower lobectomy was performed through the resected sixth

the lung. During the procedure the muscles and other tissues oozed continuously in spite of careful hemostasis. Postoperative recovery was complicated by the development of a moderate left hemothorax which was treated by aspiration, with the aid of appropriate enzymes.

Examination of the resected specimen (Fig. 3) revealed the main pulmonary artery to the left lower lobe to be 1.5 cm. in diameter and the corresponding vein 2 cm. in diameter. The artery and vein were connected by four anastomosing vessels about 0.3 cm. in diameter which, at one point, formed a sinus 3 cm. in diameter at the diaphragmatic surface of the lung. Microscopic examination (Fig. 4) revealed an increase and reduplication of elastic fibers and patchy areas of fibrous intimal thick-

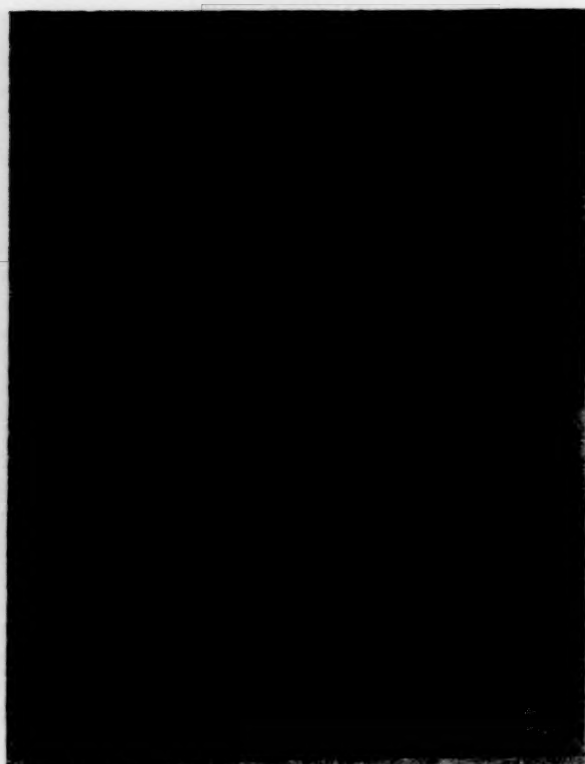


FIG. 3. Photograph of lower lobe of left lung removed at surgery showing probes in branch of pulmonary artery (A) and in pulmonary vein (V) with tips extending into large communicating chamber.

ening in the branches of the pulmonary artery leading to the fistula. The wall of the cavernous space contained an irregularly thickened and partially hyalinized fibrous intima and a few bundles of smooth muscle. The wall of the pulmonary vein contained a thick, hyalinized intima. The patient left the hospital on the fourteenth postoperative day. At that time his red blood count was 4.9 million per cu. mm., his packed cell volume 53 per cent and hemoglobin 14.0 gm.

On February 1, 1952, the patient re-entered the hospital for additional studies. He was feeling entirely well, doing his work without discomfort and could run, ride a bicycle and climb stairs easily. Physical examination revealed complete disappearance of cyanosis and a distinct decrease in clubbing. The blood pressure was 120/80 mm. Hg. Laboratory studies revealed a red blood cell count of 4.8 million per cu. mm., hemoglobin 15.8 gm. and packed cell volume 47 per cent. The MCV was 94, MCH 31 and MCHC 35. The white blood count was 8,000 per cu. mm. with a normal differential count. The platelets numbered 132,000 per cu. mm. Bleeding time was two and one-half minutes. The clot

retraction was normal. The reticulocytes were 0.5 per cent. The bone marrow was normal and megakaryocytes were abundant. The electrocardiogram was normal and x-rays of the chest revealed a decrease in the size of the heart and pulmonary arteries since the preoperative examination. Cardiac catheterization studies (Table 1) revealed normal intracardiac pressures and an arterial oxygen saturation of 90 per cent.

RESULTS AND COMMENTS

The results of the physiologic studies are summarized in Tables I and II and Figure 5.

Preoperatively at rest the oxygen consumption was moderately increased by 27 per cent. The cardiac output was slightly elevated and the peripheral arteriovenous difference was normal. The right ventricular pressure was normal. Over half of the output of the right ventricle passed through the fistula and thus reached the left auricle without being oxygenated. This resulted in a decreased arterial oxygen saturation. Anoxia of the bone marrow produced an increase in red cell production resulting in a striking elevation of the packed cell volume and an increase in blood volume due entirely to an increase in the total number of red cells. These data are similar to the results obtained in seven previously reported cases of pulmonary arteriovenous fistula. (Table II.)

Of particular interest was the effect of exercise upon the circulation in this patient. The cardiac output did not increase but actually fell slightly despite an amount of exercise which increased the oxygen consumption by 50 per cent. The cause of this failure of cardiac output to increase was not apparent. It was not related to any change in pulmonary vascular resistance since the right ventricular pressure was only slightly higher and the increase in the calculated total pulmonary vascular resistance was only 12 per cent. It was not due to heart failure since there was no evidence of clinical congestive failure and the resting diastolic pressure in the right ventricle was normal and indeed fell slightly during exercise. It was not related to arterial anoxia, since there was no fall in the peripheral arterial saturation. Further studies on additional patients will be necessary to understand this phenomenon.

During exercise the calculated flow through the fistula decreased while the flow through the pulmonary capillary bed increased. Since



FIG. 4. Photomicrograph of a portion of fistula (Van Gieson's stain $\times 90$) showing irregular cavernous spaces lined by endothelium. Note irregular intimal thickening (A) and underlying supporting stroma of elastic and collagenous tissue.

this occurred in the presence of a slight fall in cardiac output, the vascular resistance of the fistula apparently increased while that of the remaining vascular bed of the lung decreased slightly. Calculation of the separate resistances, as summarized in Table 1, supports this concept. The cause of the increased resistance of the fistula during exercise is not evident but it could be due to increased turbulence, constriction of arteries or veins connected to the fistula, or possibly also constriction of the fistulous tract since smooth muscle fibers were demonstrated in its wall.

Whether this failure of arterial oxygen saturation to fall during exercise is a unique phenomenon or occurs often in cases of pulmonary arteriovenous fistula is unknown. In the case reported by Maier et al.⁹ the arterial oxygen saturation fell from 74 to 59 per cent during activity. Denolin and his workers¹² also noted a fall in saturation during exercise as measured by the oximeter but no figures are given. Catheterization studies were not made during exercise in these cases hence it is not possible to calculate the flows through the lung or the magnitude of the shunts.

The alterations in the circulation produced by surgery are important since the relatively normal postoperative arterial oxygen saturation sug-

gests that all of the fistula was removed. Postoperatively the cardiac output increased during exercise and the peripheral arteriovenous difference was lower both at rest and during activity. This suggests that the cardiac inefficiency noted preoperatively was due to the presence of the fistula and that it may be present in the absence of any clinical or physiologic evidence of congestive failure. The right ventricular pressures were distinctly lower after surgery, both at rest and during exercise. This may be related to the striking decrease in the packed cell volume and blood viscosity, which will affect peripheral resistance particularly when the packed cell volume becomes greater than 60 per cent.¹⁶ The marked fall in blood volume was largely a result of a reduction in red cell volume. The mechanism of the destruction and removal of such a large number of red cells has been studied elsewhere¹⁷ and is accomplished by normal processes. The low platelet count prior to surgery was striking. There was no history of drug ingestion to indicate a secondary thrombocytopenia and the megakaryocytes in the bone marrow specimens obtained by biopsy and puncture appeared to be normal. In spite of the low platelet count the bleeding time was only slightly prolonged (six and one-half minutes) using the Duke method, but colt

retraction was definitely retarded. These hematologic changes may have been responsible for the excessive bleeding noted at surgery as well as for the occurrence of the postoperative hemothorax. Thirteen days after surgery the bleeding time was normal (two and one-half

SUMMARY

Physiologic observations were made at rest and during exercise in a patient with a large, solitary pulmonary arteriovenous fistula. The studies were repeated after excision of the lesion.

The significant preoperative findings con-

TABLE II

COMPARISON OF DATA FROM PHYSIOLOGIC STUDIES IN PATIENTS WITH PULMONARY ARTERIOVENOUS FISTULAS INCLUDING THE PATIENT REPORTED IN THIS PAPER (CASE 8)*

No.	Age	Sex	Surface Area (M ²)	Arterial Saturation %	Pulmonary Artery Pressure (mm. Hg)	Packed Cell Volume %	Cardiac Output (cc./min./M ²)	Effective Pulmonary Flow	Fistula Flow	Cardiac Output through Fistula %	Peripheral Resistance Lung Total (mm./Hg/L. min./M ²)	Peripheral Resistance with Fistula	Peripheral Resistance Less Fistula
1	24	M	1.80	86	17	66	3,400	1,980	1,720	42	3.2	7.8	5.6
2	15	M	1.18	68	19	79	2,580	760	1,520	71	3.0	9.7	4.3
3	28	F	1.41	76	23	77	4,170	1,010	3,160	76	2.5	10.5	3.4
4	8	F	0.97	61	20	53	3,880	1,530	2,350	61	4.5	11.5	7.5
5	20	F	74	12	70	3,240	1,360	1,880	58	7.8	5.0	3.7
6	27	M	1.57	73	14	90	7,700	1,660	6,040	80	5.2	2.4	.66
7	19	M	1.4†	85	..	54	4,900	2,700	2,200	45
8R	23	M	1.98	80	16	83	3,900	1,820	2,080	53	1.6	3.1	3.5
8E	82	18	..	3,700	2,280	1,420	38	1.8	4.8	3.0

* Cases 1 to 5 from Friedlich,¹¹ Case 6 from Baker¹⁰ and Case 7 from Denolin.¹² R = rest; E = exercise.

† Assumed normal valve.

minutes) and clot retraction was normal. The possibility that the thrombopenia was related to the pulmonary arteriovenous fistula is suggested by the sustained rise of the platelet count to

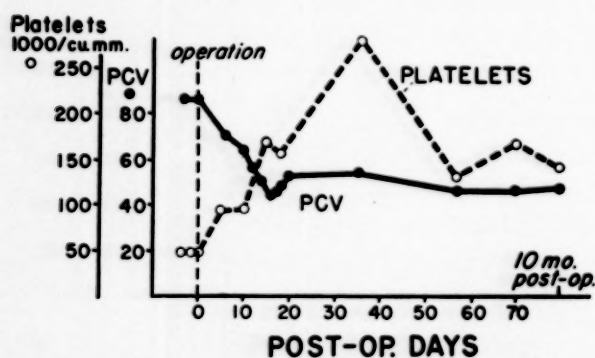


FIG. 5. Graphic summary of changes in packed cell volume and platelet count occurring after surgery.

normal levels after operation, as indicated in Figure 5. The occurrence of hemorrhagic phenomena with thrombocytopenia has been noted by others¹⁸ but the mechanism of the hematologic alterations is unknown.

sisted of: (1) intracardiac pressures which were normal in the presence of a blood flow through the fistula amounting to 53 per cent of the cardiac output; (2) failure of the cardiac output to increase during exercise, the pulmonary artery pressure remaining low, the blood flow through the fistula decreasing and the flow through the pulmonary capillary bed increasing. This was accompanied by no significant change in the arterial oxygen saturation.

Postoperatively the circulation at rest and the response to exercise were essentially normal.

Inability to increase cardiac output during exercise was not due to congestive failure, increase in total pulmonary vascular resistance or changes in arterial oxygen saturation. The failure of the arterial oxygen saturation to fall during exercise is unusual and may be due to changes in the separate resistances of the pulmonary vascular bed and the fistula. These data suggest further study of patients with this lesion to understand the physiologic changes occurring with exercise.

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Cushing's Syndrome Produced by a Pituitary Basophil Carcinoma with Hepatic Metastases*

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CUSHING's syndrome is presently thought to result from continued excessive secretory activity of the adrenal cortex but the site of the initiating lesion of this disorder remains controversial. Most clinical and experimental observations of recent years point to a lesion of the adrenal cortex consisting either of primary hyperplasia or neoplasia. Degeneration of the paraventricular nuclei of the hypothalamus has been observed and has been suggested as the initiating factor. These findings contrast with Cushing's original concept that adenomas of the basophil cells of the adenohypophysis are the primary lesion. These tumors are not found consistently and it has been doubted that they are true neoplasms. There are, however, on record rare instances of Cushing's syndrome in which the presence of malignant tumors of the adenohypophysis suggests that the disorder may at times originate in the pituitary. Our patient appears to belong in this small group. She was a young Negress with classic Cushing's syndrome in whom at autopsy a basophil cell carcinoma of the adenohypophysis with metastases to the liver was present.

CASE REPORT

A twenty-six year old Negress had been in good health until September, 1948, when she gradually began to gain weight. She had been delivered of a normal child after uneventful pregnancy in March, 1948. Her menses became scanty and stopped completely in January, 1949, at which time she began to suffer from recurrent severe generalized headaches associated with scotomas, nausea and vertigo. By August, 1949, she had gained 70 pounds in

weight. She came to the outpatient clinic of Grady Memorial Hospital at that time because of increasing exertional dyspnea and failing vision. Her weight was 203 pounds and her blood pressure 170 mm. mercury systolic and 100 mm. diastolic. She had bilateral lenticular opacities. The physical examination was otherwise not remarkable except for advanced lesions of granuloma inguinale of the vulva. Laboratory examination showed 1 + albuminuria and 15-20 white blood cells in the urinary sediment. In November, 1949, she was admitted to the medical ward because of lobar pneumonia which responded promptly to penicillin therapy. Examination at that time showed rounding of the face, purple striae over the abdomen, severe obesity and hypertension. A diagnosis of Cushing's syndrome was made but not confirmed since the patient had to be discharged.

She was not seen again until August, 1950, when she injured her right foot with a pitchfork. The wound failed to heal and she returned to the hospital on October 28, 1950. She was given 1,500 units of tetanus antitoxin subcutaneously and promptly collapsed in shock. Supportive therapy with oxygen and intravenous digitoxin restored her blood pressure to its usual elevation of 180/100 mm. mercury. She was admitted to the Medical Service.

Physical examination showed the pulse to be 90 beats per minute, respirations 28 per minute and temperature 98.0°F. The blood pressure was 180/100 mm. mercury in both arms. The patient was very obese, lethargic and orthopneic. Her face was rounded and accumulations of fat over the shoulders and trunk were more prominent than in the extremities. The face and neck

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FIG. 1. The patient three years before death.



FIG. 2. The patient during her terminal illness.

were abnormally hirsute. (Figs. 1 and 2.) The abdomen was covered with numerous wide purple striae which extended over the flanks and hips. There were bilateral lenticular opacities, a right internal strabismus, and inequality and irregularity of the pupils which were persistently contracted. Light perception was present in the left eye; the right was completely blind. It was impossible to visualize the optic fundi. The heart was markedly enlarged, extending to the anterior axillary line but was otherwise unremarkable. Granuloma inguinale still involved the vulva. The ankles and lower legs were edematous and there was a deep indolent ulcer on the dorsum of the right foot.

Laboratory examination repeatedly showed 1 to 3 + albuminuria and 1 to 3 + glycosuria. The maximum specific gravity of the urine was 1.016. There were many white blood cells in the urinary sediment. The red blood cell count was consistently between 4,000,000 and 4,600,000 per cu. mm. and the blood hemoglobin concentration ranged from 11.8 to 13.1 gm. per cent. The white blood cell count was never less than 17,600 and once rose as high as 23,000 per cu. mm.; the differential count showed from 84 to 88 per cent mature polymorphonuclear leukocytes and from 8 to 12 per cent lymphocytes. The total eosinophil count was 22 per cu. mm. on two occasions. The non-protein nitrogen determinations ranged from 51 to 56 mg. per cent. The plasma proteins were 4.8 to 5.3 gm. per cent. A single serum calcium determination was 7.2 mg. per cent. Fasting blood sugar values

ranged between 166 and 423 mg. per cent. Blood electrolyte studies (Table 1) showed hypokalemia and increased serum bicarbonate with normal serum sodium and low serum chloride on admission. After therapy with a 200 mg. sodium diet and added oral potassium citrate,

TABLE 1
SERUM ELECTROLYTE VALUES, MEQ/L.

Hospital Day	K	Na	Cl	HCO ₃
5	1.5	142	83	41.5
6	1.4	141	70
11	2.4	140	..	39.2
25	5.2	138	87	28.7

4 gm. three times daily, the electrolyte values returned toward normal although the chlorides remained low. Roentgenograms revealed demineralization of the vertebral bodies but the skull was normal. Several old rib fractures with callus formation were present. Intravenous pyelograms failed to show definite evidence of a suprarenal mass.

On the eighteenth hospital day a severe epistaxis occurred which was controlled only after nasal packing. The bleeding, clotting and prothrombin time, platelet count and tourniquet test were normal. The blood hemoglobin concentration dropped from 13.1 to 6.0 gm. per cent and three transfusions of whole blood were given. The ulcer on her foot did not heal. Her

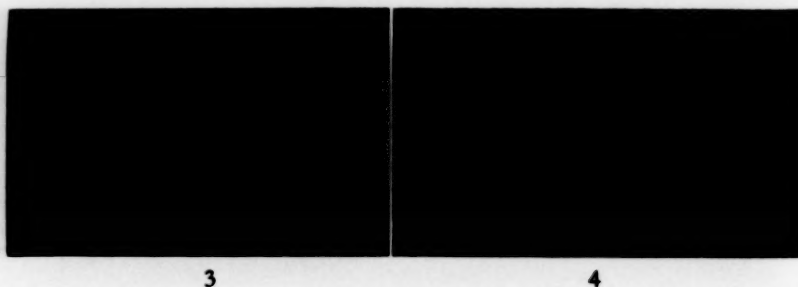


FIG. 3. Portion of sphenoid bone and the sella turcica with the pituitary *in situ*. Note the small tumor masses above the diaphragma sellae.

FIG. 4. Cut surface of pituitary after fixation. The anterior lobe is completely replaced by tumor.

vulval granuloma inguinale, however, responded rapidly to streptomycin therapy.

The patient was prepared for surgical exploration of the adrenal glands. She died suddenly during the induction of ether anesthesia twenty-seven days after admission to the hospital.

Autopsy was performed three and one-half hours postmortem.

Gross findings: The body was that of a markedly obese woman measuring 170 cm. in length. The subcutaneous fat showed a buffalo type distribution. Subcutaneous purple striae were prominent over the lower abdomen and the shoulders. The face and neck revealed excessive growth of hair but the pubic hair was absent. The labia majora were hypertrophic, edematous and scarred. The breasts were large and pendulous. A large ulcer covered the dorsum of the right foot exposing the tendon sheaths. The extremities revealed a moderate degree of pitting edema. The conjunctivae were slightly icteric. Both pupils were small and the right was irregular.

The subcutaneous fat measured from 7 to 8 cm. in thickness. On section, the breasts consisted of adipose tissue with a few small islands of parenchyma. The peritoneal cavity contained 200 cc. of slightly cloudy yellow fluid but the peritoneal surfaces were smooth and glistening. The left pleural cavity contained 100 cc. of clear yellow fluid, while the right pleural cavity was obliterated by dense fibrous adhesions. The pericardial sac and its surfaces were not remarkable.

The enlarged heart (590 gm.) showed only a few small atheromatous plaques at the root of the aorta and in the coronary arteries. The right lung weighed 570 gm., the left, 450 gm. The left apex contained a 3 cm. firm nodule which on cut surface was honeycombed and revealed a 1 cm. cavity filled with grayish green soft ma-

terial. The smaller branches of the pulmonary artery contained many firm, dark red thrombi. The cut surfaces of the lungs were dark red and moist. The hilar lymph nodes were large and anthracotic without areas of calcification. The spleen (150 gm.), esophagus, stomach and the entire intestinal tract were not remarkable. The pancreas (120 gm.) contained multiple small grayish white areas of necrosis involving the head and the proximal part of the body.

The liver (2,600 gm.) presented a smooth serosal surface of uniform light reddish tan color. The cut surfaces revealed a mottled light tan color with indistinct lobular architecture. Scattered through the parenchyma were eight well circumscribed, firm, grayish yellow nodules ranging from 2 to 15 mm. in diameter. The gallbladder and bile ducts appeared normal.

The right adrenal weighed 19.5 gm., the left 20 gm. Both organs were normal in shape and consistency. On cut surface the cortex was wide and prominent containing many ill defined light yellow nodules not exceeding 2 mm. in diameter. No tumor masses were noted. The kidneys (combined weight 390 gm.) revealed a reddish tan, finely and diffusely granular surface. The cortical and medullary markings were somewhat indistinct. The lower urinary tract was not remarkable.

The vaginal mucosa was smooth. The external cervical os presented a small erosion. The endometrium was thin. The uterus and tubes were not remarkable. The ovaries measured 3 by 2 by 1.5 cm. and showed no cystic follicles. Many firm, dark red thrombi filled the veins of the pelvic plexus. The other veins, including the venae cavae and portal vein as well as the aorta, appeared normal. Except for some enlargement of the inguinal nodes, the lymph nodes were not remarkable.

The thyroid (18.3 gm.) and a 4 mm. para-

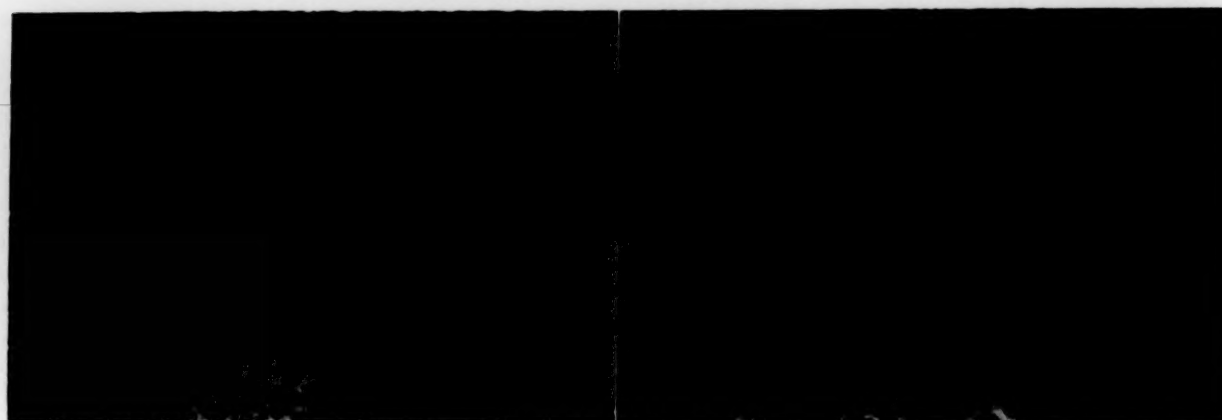


FIG. 5. Metastatic carcinoma in liver. The liver tissue (left upper corner) is invaded by the tumor. Note columnar shape of tumor cells around blood vessel (center); hematoxylin-phloxine, $\times 138$.

FIG. 6. Metastatic tumor in liver. The cells with dark cytoplasm are P.A.S. positive; trichrome-P.A.S. stain, $\times 276$.

thyroid (the only one identified) were not remarkable. The thymus consisted of a small amount of fatty and fibrous tissue. The bone marrow was dark red. The bones of the skull appeared softer than usual. The musculature was not remarkable.

The brain (1,120 gm.) showed flattening of the convolutions and a slight cerebellar pressure cone. Grossly, the optic nerves appeared normal. The cut surfaces after fixation, as well as the vessels at the base, were not remarkable. A segment of cervical and lumbar cord revealed nothing of note. The orbits were not examined.

The sella turcica and the clinoid processes were of normal size and conformation. Two soft pinkish gray masses of tissue, each measuring 3 to 4 mm., protruded above the diaphragma sellae. (Fig. 3.) The pituitary was of normal size. After fixation, when sectioned through its equator, the cut surface revealed a grayish white mass with brownish areas. This mass obliterated most of the usual landmarks of which only part of the posterior lobe could be identified. (Fig. 4.) The sphenoidal sinuses contained yellow mucoid material. The other air sinuses, the middle ears as well as the dura and its sinuses were normal.

Histologic findings: Except for hypertrophy of the individual muscle fibers, no remarkable findings were noted in the heart. Sections through the scar in the left apex of the lung revealed extensive old fibrosis with ectasia of some bronchi but no evidence of caseation or calcification. The remaining portions of the lung showed marked acute and chronic passive congestion with numerous pigment-laden large mononuclear cells in the alveoli. Many arteries

contained old and recent thrombi but there was no evidence of infarction.

In the spleen the malpighian corpuscles were depleted and the red pulp was congested. The arterioles displayed thickening and hyalinization of the media. Except for slight atrophy of the gastric mucosa, no remarkable findings were noted in the gastrointestinal tract. In the pancreas the parenchyma, interlobular and peripancreatic tissue displayed many areas of acute and subacute necrosis. The arterioles throughout showed medial thickening and hyalinization. The islets were not remarkable.

The tumor nodules in the liver consisted of epithelial cells arranged in irregularly convoluted cords and clusters. The growths freely invaded the adjacent tissues. The tumor cells were uniform in size, and their shape tended to be columnar around the small blood vessels and at the periphery of the nodules and polyhedral in the center. (Fig. 5.) The nuclei were oval, slightly pleomorphic and displayed a single small nucleolus. There was some variation in the amount and distribution of the nuclear chromatin. Mitoses were present. With Mallory's aniline blue stain¹ the cytoplasm appeared deeply basophilic and finely granular. With the trichrome-PAS method of Pearse² the cytoplasm stained dark red with innumerable fine granules (Fig. 6.) These staining reactions were most pronounced in the columnar shaped cells. In the center of the tumor masses Mallory's method stained the cytoplasm bluish gray with some scattered fine blue granules and the PAS technic revealed some fine dark red granules against an orange background. The tumors had elicited

only slight stromal response and the stroma consisted of a delicate connective tissue rich in thin capillaries. The uninvolved hepatic parenchyma displayed extensive fatty metamorphosis in the central and mid-zonal parts of the lobules. The liver cells at the lobular periphery, as well as the portal spaces and their contents, were not remarkable. There were no abnormal findings in the gallbladder.

In the adrenals the zona fasciculata was markedly widened. The zona glomerulosa appeared somewhat thinner than usual. The zona reticularis was not remarkable. The cortex revealed marked lipid depletion. Many small ill defined foci of cortical hyperplasia were present, formed largely by the cells of the zona reticularis. Areas of "tubular degeneration" were frequently found involving chiefly the peripheral portion of the fascicular zone. The medulla appeared normal. The arterioles in the adrenal capsule and periadrenal tissue revealed hyaline thickening of the media.

The glomeruli in the kidney in general displayed hyaline thickening of their capillaries which occasionally progressed to partial or complete hyalinization of the entire structure. In some instances adhesions were present between the loops and the capsule. The arterioles everywhere showed appreciable hyaline thickening of their walls. Acute fibrinoid degeneration of the afferent arterioles was encountered occasionally. This degenerative process often extended into the glomerulus where it was sometimes associated with leukocytic infiltration and hemorrhage occasionally amounting to infarction. Many tubules contained hyaline casts and some granular acidophilic precipitate. The epithelium, chiefly in the proximal convoluted tubules, was often swollen and contained some finely dispersed fat droplets. The arteries were not remarkable. The veins were congested. The interstitial connective tissue and the calyceal and pelvic tissues were not remarkable.

A small vein situated in the areolar tissue outside the bladder wall contained a recent antemortem thrombus. The bladder proper was not remarkable. In the genital tract, the endometrium was atrophic. The ovaries showed many primary follicles but no graafian follicles. There were numerous corpora albicantia but no corpora lutea. The vulva revealed marked old fibrosis and some residual chronic inflammation but no evidence of granuloma inguinale.

Only rare islands of atrophic parenchyma were seen among the adipose tissue of the breast. The thyroid gland showed no abnormalities. The general architecture of the parathyroid was normal. Water-clear cells represented the most frequent component. The remaining cells were chief cells and rare oxyphils.

Occasional foci of medial cystic necrosis were seen in the aorta. There were no other significant findings. Sections of skin from the abdomen showed a thin epidermis with little cellular proliferation in the basal layer. The collagen bundles of the corium were also thin and widely separated. Sections representing the ulcer of the foot revealed practically complete absence of regenerative proliferation of the epidermis at the edges. The ulcer base consisted of a thin layer of poorly developed granulation tissue with a few chronic inflammatory cells. Capillaries were sparse and small and there was hardly any proliferation of fibroblasts. Deeper, the ulcer was surrounded by condensed inactive appearing fibrous tissue.

Peripheral striated muscle and peripheral nerve showed no remarkable findings. The lymph nodes were normal except for marked lymphoid depletion. Sections of calvarium, vertebra and rib revealed marked thinning of both cortical and trabecular bone without appreciable osteoblastic or osteoclastic activity. The bone marrow revealed secondary hyperplasia. In the brain and spinal cord, perineuronal edema and oligodendroglial swelling were the only findings. The floor of the third ventricle showed no tumor invasion. No changes were noted in the paraventricular nuclei of the hypothalamus. Sections through the optic nerves distal to the chiasm and before their entry into the orbits showed no tumor invasion.

The anterior lobe of the pituitary was almost entirely replaced by tumor tissue composed of medium size epithelial cells arranged in irregular columns and clusters. (Fig. 7.) At the periphery of the tumor masses and often around the small blood vessels the cells were columnar in shape while more centrally they were polyhedral. (Fig. 8.) The nucleus was generally oval with an inconspicuous nucleolus. There was some variation in the distribution of nuclear chromatin. Mitoses were fairly frequent. The ample and homogeneous cytoplasm stained grayish or amphophilic with hematoxylin-phloxine. The cytoplasm stained granular and deeply basophilic with Mallory's aniline blue method and dark

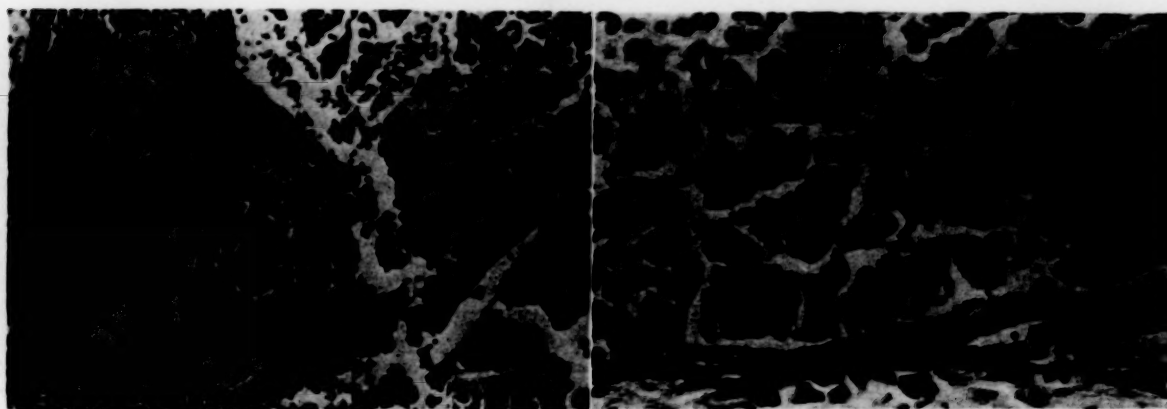


FIG. 7. Pituitary carcinoma. The general architecture and cytologic detail are the same as seen in the liver metastasis (Fig. 5.); hematoxylin-phloxine, $\times 138$.

FIG. 8. Pituitary carcinoma. Note the columnar shape of the cells; hematoxylin-phloxine, $\times 276$.

red with granules with the trichrome-PAS technic of Pearse. (Fig. 9.) These staining reactions were seen in most columnar and many of the polyhedral cells. In the remaining cells Mallory's method showed a bluish gray cytoplasm with some fine blue granules and the PAS technic stained the cytoplasm orange with many dark red granules.

The neoplastic tissue was divided into ill defined lobules by strands of dense connective tissue with a few hemosiderin deposits. The lobules possessed a delicate connective tissue stroma rich in capillaries which showed occasional lacunar dilatations. Tumor cells freely invaded the intermediate portion, the posterior lobe, the inferior portion of the stalk and the capsule. Frank invasion of small veins was a frequent finding.

A small amount of non-neoplastic adenohypophysis remained near the superior and posterior portion of the anterior lobe. The basophilic cells were numerous but most of them showed Crooke's change with both Mallory's or the PAS stain sometimes with small vacuoles. No changes were noted in the acidophilic cells while chromophobe elements appeared to be diminished in number.

Nests and cords of the neoplasm were seen to invade extensively the Gasserian ganglia and surrounding connective tissue as well as veins, nerves, nerve sheaths and the adventitia of the internal carotid arteries. The bone and mucosa of the ethmoid sinuses revealed extensive invasion by the growth. In the bone the tumor replaced the marrow, producing some resorption of bone trabeculae.

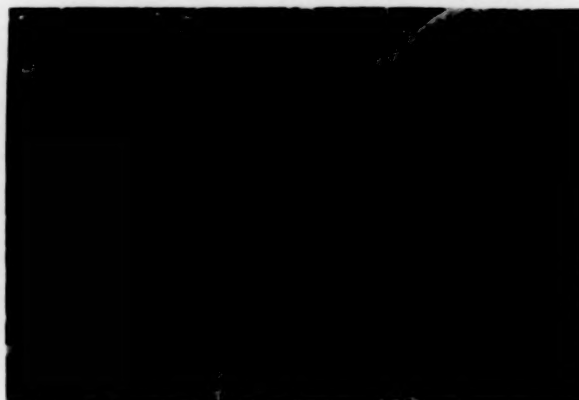


FIG. 9. Pituitary carcinoma. The cytoplasm of most cells is P.A.S. positive; trichrome-P.A.S. stain, $\times 276$.

Anatomic diagnosis: Basophil cell carcinoma of adenohypophysis with bilateral extension to Gasserian ganglion, invasion of mucous membrane and bone of sphenoid sinuses and of blood vessels and with multiple metastases to liver; Crooke's change in uninvolved portion of adenohypophysis; Cushing's syndrome with obesity, hirsutism and subcutaneous striae; hyperplasia of adrenal, bilateral (39.5 gm.); osteoporosis, marked; hyperplasia, secondary, of parathyroid; generalized arteriosclerosis; arteriolonephrosclerosis with necrotizing arteriolitis; cardiac hypertrophy (590 gm.); acute and subacute pancreatitis; fatty metamorphosis of liver, marked; icterus; ascites (200 cc.); atrophy of endometrium, ovaries and breasts; indolent ulcer of right foot; medial cystic necrosis of aorta; thrombosis of veins of pelvic plexus; pulmonary emboli, multiple; hydrothorax, right (100 cc.); chronic passive congestion of viscera; cerebral edema; old scar, apex left

lung; pleural adhesions, fibrous, left; fibrosis, marked, of vulva.

COMMENTS

Several reviews in recent years have evaluated the evidence concerning the initial lesion of Cushing's syndrome.³⁻⁵ On the basis of many studies, the concept of the adrenocortical origin of the disorder has been widely accepted, although many authors agree that final proof is lacking.

Following the introduction of ACTH and cortisone into clinical practice it was noted that these substances could produce manifestations closely resembling Cushing's syndrome. It was also shown that both ACTH and cortisone produced basophilism and Crooke's hyaline change in human pituitaries.^{6,7} Finally, it became possible to induce Crooke's change in the rat pituitary by the administration of these hormones.⁸ These findings lent further support to the concept of the adrenocortical origin of Cushing's syndrome.

Rare instances of Cushing's syndrome are described in which it is difficult to attribute the disorder to primary adrenocortical hyperfunction. In these patients primary neoplasms of the adenohypophysis were present. Basophil adenomas will not be considered in this context since their neoplastic nature is open to question.

Our patient presented the classic findings of Cushing's syndrome. These were: moon face, buffalo type obesity, hirsutism, abdominal striae, hypertension, diabetes, amenorrhea, osteoporosis and delayed wound healing. Chemical studies showed glycosuria, hyperglycemia and slight azotemia as well as hypokalemia and alkalosis.

The principal autopsy findings consisted of an adenocarcinoma of the adenohypophysis with bilateral invasion of the Gasserian ganglia and the mucous membrane of the sphenoid sinus, and multiple liver metastases. The adrenals showed bilateral hyperplasia (39.5 gm.) The tumor cells in the adenohypophysis and in the liver were identical in their architectural arrangement, size, shape and nuclear as well as cytoplasmic characteristics. The cells of the pituitary tumor were readily identified as basophils. These cells contained distinct cyanophilic granules when stained with Mallory's aniline blue.¹ The same cells reacted positively with the trichrome-PAS method as applied by

Pearse.² The tumor cells in the liver displayed identical staining reactions. In both the adenohypophysis and the liver, cyanophilia and PAS-positive reactions were most conspicuous in neoplastic cells of columnar shape, found at the periphery of the tumor columns and clusters. These staining reactions were also present in the cells in the center of the tumor nodules. Here the cells appeared more like transitional basophils or intermediate mucoid cells.

Crooke's hyaline change was frequently encountered in the basophils of the residual portion of the uninvolved adenohypophysis. It was observed with both the Mallory and Pearse methods but appeared more widespread in the Mallory preparations. Furthermore, a number of the neoplastic cells in both the pituitary and the liver showed cytoplasmic hyalinization with Mallory's stain. They did not, however, have the characteristics of Crooke's change in preparations stained with the Pearse method.⁹

The diagnosis of carcinoma of the basophil cells of the adenohypophysis with metastases to the liver in our patient is based upon the described morphologic, tinctorial and histochemical observations.

Cohen and Dibble¹⁰ have reported a woman with well documented Cushing's syndrome who at autopsy showed findings strikingly similar to those we have described. In their patient a carcinoma of the basophil cells of the adenohypophysis was found with several small metastases in the liver. These authors also comment on the columnar shape of the neoplastic cells which is well illustrated by their text figures 9 and 14. It is of interest that the authors mention an ulcer of the right leg described as indolent. Crooke's change was not described either in the tumor or in the residual uninvolved adenohypophysis.

A patient with an adenocarcinoma of the adenohypophysis with multiple liver metastases has been described by Forbes.¹¹ It was stated that the patient had Cushing's syndrome but the clinical and laboratory data included in the report are scant. The pituitary tumor was composed primarily of chromophobe cells with some acidophilic elements. Crooke's change was seen in the uninvolved adenohypophysis. The metastatic nodules in the liver consisted entirely of acidophilic cells.

Feiring and co-workers¹² have published a study on primary carcinoma of the pituitary. The authors describe a woman with the clinical

manifestations of hypopituitarism and a histologically proven chromophobe tumor of the adenohypophysis in whom Cushing's syndrome subsequently developed. At autopsy a chromophobe cell carcinoma of the adenohypophysis was found with three metastatic foci involving the dura of the anterior cranial fossa. There were no other primary neoplasms. The basophils of the uninvolved adenohypophysis showed Crooke's hyaline change.

Does the finding of primary malignant tumors of the adenohypophysis indicate that this organ may at times be the site of the initiating lesion of Cushing's syndrome?

Pituitary changes consisting of basophilism and Crooke's hyaline change have been constant findings in Cushing's syndrome, although their significance has remained uncertain. Several observations, however, point to a relationship of the basophil cells to ACTH metabolism. These cells are increased in number in Cushing's syndrome and decreased or absent in Addison's disease. The administration of ACTH or cortisone to patients produces pituitary basophilism, as well as a clinical picture resembling Cushing's syndrome.^{6,7} Finally Marshall, using the fluorescent antibody technic, has localized adrenocorticotrophin in the pituitary basophils.¹³

In the patients reported by Forbes¹¹ and by Feiring and co-workers¹² the pituitary tumors were not composed of basophil cells and might be regarded as incidental findings. On the other hand, a relationship between the pituitary neoplasms and Cushing's syndrome is quite probable in the patients reported by Cohen and Dibble¹⁰ and by us, since in these instances both the pituitary tumor and its metastases were composed of basophil cells. It appears, therefore, that in exceptional instances the adenohypophysis may be the site of the initiating lesion.

Numerous instances of Cushing's syndrome associated with primary benign or malignant neoplasms of the adrenal cortex have been reported. The initiating role of these neoplasms is shown by the regression or disappearance of the disease following surgical extirpation.^{4,5}

In a large number of patients with Cushing's syndrome the morphologic findings consist of bilateral adrenocortical hyperplasia and pituitary basophilism. The significance of either lesion is not clear since adrenal cortical hyperplasia can be produced by ACTH administration and pituitary basophilism may be induced by either exogenous ACTH or cortisone. It is

apparent that in these cases adrenocortical hyperplasia and pituitary basophilism might merely represent a secondary morphologic expression of an altered anterior pituitary-adrenal cortex balance, rather than the primary initiating factors. The problem of the site of primary disturbance in these patients might be resolved by the determination of pituitary adrenocorticotrophin production in patients with bilateral adrenal cortical hyperplasia. The presence of high circulating adrenocorticotrophin would indicate the primary role of the anterior pituitary whereas a decrease of circulating adrenocorticotrophin in the presence of high blood corticoid levels would point to a primary disturbance of the adrenal cortex. A number of observations concerning circulating adrenocorticotrophin have been reported but the results are too contradictory to permit conclusions.¹⁴⁻¹⁷

It appears that Cushing's syndrome represents the effects of an altered adenohypophyseal-adrenocortical balance. The site of the primary disturbance may in rare instances be in the adenohypophysis, as suggested by our patient, but more frequently it can be localized in the adrenal cortex. In a large number of patients, however, the initiating lesion cannot at present be determined.

SUMMARY

A basophil cell carcinoma of the anterior pituitary, with multiple liver metastases, was found at autopsy in a young Negress with classic Cushing's syndrome. These findings indicate that in rare instances the adenohypophysis may be the site of the initiating lesion of this disorder.

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Cruveilhier-Baumgarten Syndrome*

Review of the Literature and Report of a Case

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IN 1833 Pegot¹ described, in an alcoholic soldier, a slight murmur over subcutaneous abdominal varices. Necropsy revealed a large spleen, "small liver" and a "patent umbilical vein." An account of this case was also published by Cruveilhier² in 1835. A more detailed description of the venous hum sometimes occurring in cirrhosis was given in 1868 by Trousseau and Sappey³ who, at necropsy of such a case, dissected the portosystemic venous anastomoses in the falciform ligament and abdominal wall. In 1907 Baumgarten⁴ reported a case of a sixteen year old boy in whom the clinical and pathologic findings were similar to those reported by Cruveilhier. The name "Cruveilhier-Baumgarten cirrhosis" was introduced in 1922 by Hanganutz.⁵

Armstrong and associates⁶ in 1942 made an extensive review of the literature, tabulated the pertinent data of fifty-two previously reported cases and added three more cases. Prior to 1942 ten other cases of this syndrome had been recorded by various authors.⁷⁻¹¹ Since Armstrong's review twenty more cases¹²⁻²⁹ have been published, bringing the total number now reported to eighty-five. The purpose of this article is to report another instance of this syndrome.

CASE REPORT

A fifty-two year old white man was admitted to the Cook County Hospital on August 6, 1953, with the chief complaints of sudden onset of weakness, dizziness and cold sweats followed by passage of two tarry stools twenty-four hours before.

There was no past history of illness until 1943 when he had a "bloody dysentery" while in a concentration camp in Germany. In 1945 a slightly prominent and tortuous vein was noted

by the patient over the lower abdomen, but he attributed it to the innumerable physical torments he received during the period of imprisonment. Since he felt well otherwise, no attention was paid to it. In 1948 the patient had some mild epigastric pain lasting several weeks. X-ray films of the gastrointestinal tract were taken and a diagnosis of gastritis was made by the German doctor in the concentration camp. In 1949 the patient had an episode of icterus and was told he had "liver trouble." Because of occasional epigastric distress x-ray films of gastrointestinal tract were obtained twice that year and both series were reported to be normal except for a small traction diverticulum at the level of the tracheal bifurcation. Since 1950 the patient had remained fairly well except for occasional heart burn and postprandial fullness. No melena was observed at anytime.

The patient drank alcoholic beverages very moderately. His nutritional status was poor during the years he was interned.

On examination the patient was found to be a well developed but rather poorly nourished white man who appeared slightly pale. The body temperature was 98°F, by mouth, the pulse rate was 80 per minute, respiratory rate 24 per minute, and the blood pressure 120/80. There was no icterus of the sclera. The chest was clear. The heart was not enlarged, had a regular rhythm and there was no murmur.

The abdomen was scaphoid, soft and non-tender. The liver was palpable 5 cm. below the right costal margin, soft and non-tender, and its edge was even and blunted. The spleen was readily palpable to 3 cm. below the left costal margin and firm in consistency. No ascites was demonstrable. Beginning from about 2 cm. above the umbilicus and slightly to the left,

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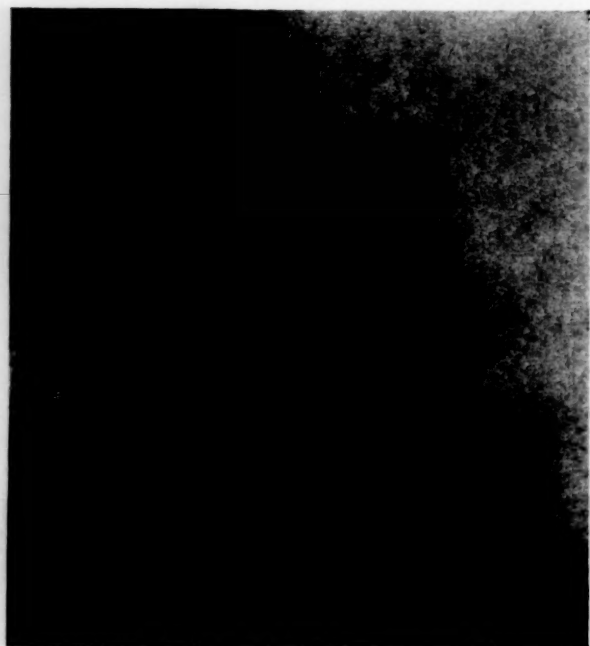


FIG. 1. Photograph of the abdominal wall vein. A, direction of blood flow; B, maximal intensity of the murmur and the thrill.

several cirroid prominent veins were seen; they joined below the umbilicus to form one prominent tortuous vein coursing down the abdominal wall mainly over the left rectus muscle, crossing the inguinal ligament at about its middle and disappearing just beneath it. (Fig. 1.) No caput medusae was present. The vein filled from above and was made particularly prominent by forced expiration against a closed glottis. A continuous loud, roaring murmur, reminding one of a train rushing through a tunnel, was heard over a penny-sized area 2 cm. below and to the left of the umbilicus, where it was maximal in intensity. The murmur was also audible with diminishing intensity over a trapezoid area bounded laterally by the prominent tortuous vein, superiorly by a line drawn through the umbilicus, inferiorly by the pubic bone and medially by the linea alba. It could also be heard faintly just across the middle line. (Fig. 2.) Light digital palpation over the site of maximal intensity revealed a continuous thrill. The murmur was more or less continuous, and had no systolic or diastolic accentuation. It became slightly louder with deep inspiration and waned during expiration, but became strong again toward the end of expiration. The murmur disappeared with increasingly firm pressure by the stethoscopic piece. Pressure just below the site of maximal intensity over the vein definitely

reduced the intensity of the murmur but did not obliterate it entirely. Pressure applied further down the course of the vein did not seem to alter the intensity of the murmur, nor did pressure applied above the site of maximal intensity. The murmur could be made to disappear entirely



FIG. 2. Distribution and intensity of the murmur.

by making the rectus contract. When the rectus relaxed again, the murmur could be heard to return gradually in a hesitant and whining manner until it resumed its loud continuous roaring character again. The murmur was not affected by change of position.

A sound tracing of the para-umbilical murmur with the stethoscopic piece placed over the site of maximal loudness and a concomitant electrocardiogram were made. (Fig. 3.) The continuous quality of the murmur was again noted.

Laboratory studies included a normal urinalysis and a negative blood Wassermann reaction. The stool was positive for occult blood by the benzidine test. The hemoglobin was 56 per cent, and the red blood count 2.82 million. The white blood count was 2,000. The differential count was 61 per cent segmented, 3 per cent non-

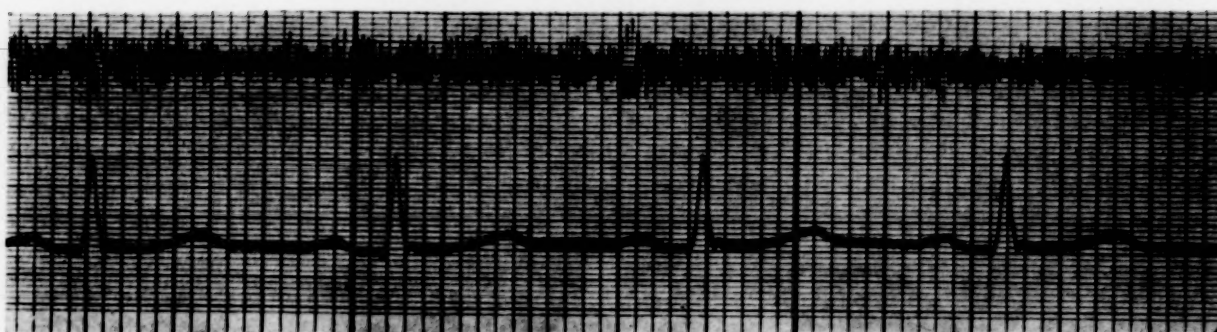


FIG. 3. Sound tracing of the umbilical murmur and simultaneous electrocardiogram. Note the continuous nature of the murmur.

segmented polymorphonuclear leukocytes, 28 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. Platelet count was normal. Blood non-protein nitrogen was 41 mg. per cent. Total protein was 6.2 gm. per cent, total cholesterol 300 mg. per cent, serum phosphorus 3.4 mg. per cent, alkaline phosphatase 3.5 Bodansky units per cent, gamma globulin 1.2 gm. per cent, thymol turbidity 4.3 units and cephalin-cholesterol flocculation test negative.

jected subcutaneously. Blood counts were repeated at ten-minute intervals until the pulse, blood pressure, respiration and splenic contraction reached their maximum stimulation and then were continued at fifteen-minute intervals until the spleen had relaxed. The results are tabulated in Table 1. At the height of the adrenalin stimulation—as shown by the maximal splenic contraction, rise of blood pressure and increase in pulse and respiratory rate—the

TABLE 1

	Blood Pressure	Respiration	Pulse	Spleen	White Blood Count	Red Blood Count	Hg (%)
Before adrenalin	112/80	22	92	3 cm.	1,900	3,300,000	58
After adrenalin							
10 min.	122/68	24	96	2.5	6,400	60
20 min.	134/70	28	108	2.2	9,900	59
30 min.	122/64	28	108	2.2	8,400	60
45 min.	116/64	24	96	3.0	6,800	60
60 min.	112/60	22	96	3.1	2,600	3,390,000	60

A bromsulphalein test using a dosage of 2 mg. per kilo of body weight showed 6 per cent retention at the end of thirty minutes. The prothrombin time was normal.

The sternal bone marrow was moderately cellular. Megakaryocytes were normal. The nucleated red cell to white cell ratio was approximately 1:1. Erythropoiesis was normoblastic. Granulopoiesis was intact. Eosinophils, lymphocytes and plasma cells were slightly increased.

An "adrenalin test" was done as follows: during a fifteen- to thirty-minute baseline period, under basal metabolic conditions, the pulse, blood pressure, respiration and preliminary complete peripheral blood studies were obtained and the splenic outline was traced. Epinephrine chloride, 0.5 cc. of a 1:1000 solution, was in-

jected subcutaneously. Blood counts were found to have risen from 1,900 to 9,900 while the red cell count, hemoglobin and platelet count remained the same.

Roentgenogram of the chest did not disclose any abnormality except for an old healed fracture of the left second rib. Roentgenologic examination of the esophagus and stomach revealed no varices or other abnormalities other than a small traction diverticulum at the mid-portion of the esophagus. The stomach and the duodenum were normal. The liver and spleen shadows appeared enlarged. Barium enema examination revealed a normal large bowel. Cholecystogram revealed a normal functioning gallbladder with no visible stones.

A needle biopsy of the liver revealed normal liver cell architecture with only a few scattered small foci of round cell infiltrations and rather

conspicuous venous sinuses at places. No atrophy, fibrosis or cirrhosis were seen.

To prove that the abdominal vein communicated with the portal venous system and must therefore be directly draining the alimentary tract, a glucose tolerance test was performed.

TABLE II
BLOOD GLUCOSE LEVELS IN THE ABDOMINAL WALL VEIN
AND THE ANTECUBITAL VEIN AFTER ORAL GLUCOSE
ADMINISTRATION

Time after Glucose (Min.)	Concentration in Ab- dominal Wall Vein (mg. %)	Concentration in Antecubital Vein (mg. %)
0	130	130
30	234	189
60	200	180
100	150	140

After fasting venous samples had been drawn from both the abdominal wall vein and a left antecubital vein, 50 gm. of glucose in 50 per cent solution was given orally. Further venous samples from both sites were taken simultaneously thirty, sixty and one hundred minutes later. To facilitate more frequent sampling, drip infusions of heparinized normal saline solution were given into both the abdominal and antecubital veins. The results of the test are tabulated in Table II. It should be noted that in the fasting state the glucose concentration in the two veins was the same; and during the sixty minutes after the glucose administration the level in the abdominal vein was conspicuously greater than that of the antecubital vein, with the peak level at thirty minutes.

A venogram of the abdominal wall vein was made. (Fig. 4.) Blood flow in the vein was stopped by digital pressure applied three fingerbreadths above the inguinal ligament. A needle was introduced above and close to the point of occlusion and 20 cc. of a radiopaque solution (diodrast®) injected retrograde to the flow. The surface marking of the umbilicus was shown. (Fig. 4F.) The tortuous inferior portion of the vein (Fig. 4A) was seen to divide below the umbilicus (Fig. 4B) into three branches: one going toward the umbilicus (Fig. 4D), one going to the right and then downward (Fig. 4E), and one going upward (Fig. 4C). The branch that went upward became much attenuated at a level 2 cm. above the umbilicus (Fig. 4C), and



FIG. 4. Venogram of the abdominal wall vein. A, tortuous main part of vein; B, point of trifurcation of vein; C, continuation of the vein upward to join the lateral thoracic veins (slightly retouched); D, branch toward the umbilicus; E, branch coursing to the right; F, surface marking of the umbilicus.

could be traced along the projection of the left vertebral border as far up as the level of the first lumbar vertebra, to communicate superiorly with the lateral thoracic veins. Fig. 4B represented the point where the four veins (Fig. 4A, C, D and E) met, and was also the site where the murmur was heard loudest and the thrill palpated. The injection was unfortunately followed by complete thrombosis of the vein.

The superficial abdominal vein measured about 15 cm. long in its entire length and contained approximately 20 cc. of diodrast. This portion when emptied of its blood filled again in about three seconds. The blood flow through the abdominal wall vein was thereafter believed to be approximately 400 cc. per minute.

The patient had no bleeding during the stay in hospital and gained five pounds in weight. He was discharged in good health on September 10, 1953, with supportive therapy.

COMMENTS

The Cruveilhier-Baumgarten syndrome is a rare clinical entity characterized by the presence of unusually prominent para-umbilical veins, evidence of portal hypertension, atrophic liver,

splenomegaly and the demonstration of a venous hum, frequently with a thrill, at the site of the para-umbilical circulation.³¹ From the analysis of Armstrong and associates⁶ it appears that cases presenting the syndrome and with adequate necropsy description can be divided into two main groups. One group fulfilled the criteria of Cruveilhier and Baumgarten as instances of congenital patency of the umbilical vein and atrophy of the liver with little or no cirrhosis and splenomegaly. This combination is designated "Cruveilhier-Baumgarten disease" (in contrast to "syndrome"). In other words, congenital patency of the umbilical vein either alone (Cruveilhier) or associated with congenital hypoplasia of the portal system (Baumgarten) may constitute an individual disease entity. Armstrong et al. noted five such cases in their article, including one of their own. A review of the literature since then reveals only one additional case,¹⁸ thus bringing the total number of cases of Cruveilhier-Baumgarten disease to six. Any other disease, however, which is associated with a clinical picture of portal hypertension (generally with splenomegaly) with unusually prominent umbilical collaterals as manifested by dilated visible abdominal veins, murmur and thrill, may properly be said to present the Cruveilhier-Baumgarten syndrome. The term "Cruveilhier-Baumgarten cirrhosis," introduced in 1922 by Hanganutz and frequently used since by French authors, is undesirable and misleading since no particular type of cirrhosis has been proved to exist and neither Cruveilhier nor Baumgarten ever ascribed any importance to cirrhosis in the disease process.

It appears appropriate to our purpose to review briefly the development of the portal system and its collaterals and also the role of the umbilical vein in portal circulation. In prenatal life the paired vitelline veins from the yolk sac and the paired umbilical veins, originally from the allantois but later from the placenta, open independently into the common sinus venosum of the heart until the developing liver intercepts them and breaks them up into the anastomosing sinusoids of the liver. The left umbilical vein also maintains a direct connection with the sinus venosum by means of the ductus venosum. The right umbilical vein disappears early. As the capillaries of the liver develop into their final state, the adult portal vein takes form out of the right and left vitelline veins, and the

left umbilical vein empties into the left branch of the portal vein. Before birth most of the placental blood is shunted directly from the left umbilical vein to the atrium of the heart through the ductus venosum. Baumgarten suggested in 1908 that a congenital hypoplasia of the portal tree increases portal venous pressure which would then shunt blood through a large patent umbilical vein to the systemic veins. There is some evidence that such a situation might produce further changes in the liver. Bainbridge and Leathes³² experimenting with cats and dogs, and Rous and Larrimore³³ with rabbits, found that experimental portal vein obstruction led to atrophy with or without marked connective tissue replacement. After birth the umbilical vein atrophies within the falciform ligament to form the ligamentum teres and the ductus venosum forms the ligamentum venosum. However, the terminal portion of the umbilical vein often remains patent in otherwise normal adults, as demonstrated by Baumgarten in sixty autopsies, and is often referred to as the Rest-Kanal of Baumgarten.³⁴ The Rest-Kanal is often utilized in collateral circulation in portal hypertension in addition to the usual potential collateral connections of the para-umbilical veins with the thoraco-abdominal veins. The whole umbilical vein occasionally may remain patent and the association of this finding with atrophy of the liver, large spleen and portal decompensation was first described by Pegot¹ and Cruveilhier.² In either instance the excessive development of collateral circulation around the umbilicus in a patient with portal hypertension of whatever cause may lead to a clinical picture reported as an example of Cruveilhier-Baumgarten disease.

To date, the demonstration in a living person of a patent umbilical vein and its communication with the portal system has proved difficult and inconclusive. Venogram with a radiopaque dye had been successfully carried out by Celis and associates³⁵ who were the first to utilize this technic for the *in vivo* demonstration of patency of the umbilical vein and its connection with the portal system. Another ingenious method of confirming the clinical diagnosis of a superficial vein as a portal-anastomotic channel is a simple biochemical method first suggested by Sherlock and Walshe.³⁶ If the abdominal vein communicates with the portal venous system, its blood must drain the alimentary tract. In our case the

conspicuously greater level of blood glucose in the abdominal wall vein than in the antecubital vein during the sixty-minute interval after glucose was given by mouth confirmed beyond doubt the clinical impression that the abdominal vein actually communicated with the portal vein. This is the second case in the literature in which this biochemical method of establishing the diagnosis of a portal anastomotic vein was employed.

It is suggested, on both clinical and radiographic grounds, that in our patient some of the portal blood entered a para-umbilical vein, or its like, to merge through a small para-umbilical hernia and join the superficial inferior epigastric vein which in turn joins the great saphenous vein just below the inguinal ligament. This vein also joins superiorly with the lateral thoracic veins, tributaries of the axillary veins. This latter communication is readily seen on the venogram (Fig. 4C).

Total blood flow through the liver in man is estimated³⁷ at 1,085 to 1,845 cc. per minute per 1.73 M² of body surface, with an average flow of 1,497 cc. Of this 12 to 25 per cent is from the hepatic artery. The anastomotic abdominal vein was estimated to carry about 400 cc. per minute. It can therefore be assumed that the collateral abdominal channel was carrying one-half to one-quarter of the portal venous blood directly into the left great saphenous vein.

In the clinical diagnosis the murmur is of great importance, and it is the presence of the unusual murmur in these cases that differentiates them from other diseases of the liver and gives them the label of the Cruveilhier-Baumgarten syndrome. The presence of this murmur is so pathognomonic of the syndrome that Bloom²⁶ stated that its presence "makes laboratory tests for liver function, including liver biopsy with its attendant changes, largely unnecessary for establishing the diagnosis." The murmur is dependent upon the formation of anastomoses between the portal and systemic circulation. Thayer³⁸ reviewed the venous murmurs in cirrhosis and classified them according to site and dilated collateral veins of origin. Armstrong *et al.*⁶ gave a comprehensive discussion on the various reported means of utilization of the umbilical vein in portal collateral circulation as well as the more usual connections through the para-umbilical veins. Recently Bloom²⁶ rendered an excellent account of the history of and clinical observations on venous hums in cirrhosis. The

murmur is definitely of venous origin. In nineteen cases reported in the literature of abdominal bruits and thrills during life in patients with portal hypertension, none exhibited an arterio-venous communication.³⁹ The murmur is loud and continuous and has been described as a roar, a "mill-like" murmur, a hollow spinning-wheel sound, a grinding sound, the sound of a high wind blowing around a corner, or a whining murmur.¹⁵ The character and intensity of the murmur are usually not influenced by the cardiac cycles, although accentuation may occur during systole²⁶ or, rarely, in diastole.⁴⁰ Fluctuation of the murmur usually occurs with the phases of respiration. Change of posture may or may not alter the intensity of the murmur. The murmur is usually localized to the region of the umbilicus or to the xiphoid process,²⁶ but radiation may sometimes be considerable. A number of cases have been reported in which transmission of the hum occurred upward over the sternal region.^{7,9} Occasionally the thoracic distribution is the salient feature. It is particularly in these cases that confusion may arise, the most frequent error being a diagnosis of congenital heart disease, as pointed out by Gwyn.⁷ Occasionally more than one focus of sound may be present.⁶ A thrill is often present at the site of maximum intensity of the hum and is usually detected by light finger pressure. Both the hum and the thrill can be made to disappear with firm pressure. The mechanism of the production of the murmur is still unsettled, although its dependence upon the venous anastomoses is beyond doubt. Gambarati,⁴⁰ Bates¹⁰ and others have considered the murmur to arise in the inferior vena cava narrowed by perivenous hepatic fibrosis. This view is not substantiated by necropsy findings, the vessel being invariably normal. Thayer³⁸ emphasized the superficial origin of the phenomenon. He considered it to be produced by blood passing under pressure through the varying caliber of the abdominal varicosities, either from small vessels into large ones or vice versa, or indeed the passage of blood through a single vessel with varicose dilatations. The readily palpable thrill would certainly suggest that the veins in which the vibration arose must have been in or in close apposition to the abdominal wall. This is the view of Lemicre and Garcin⁸ and Hall.⁹ Armstrong *et al.* proposed that the murmur is due to the "passage of blood to an area of different caliber or direction, or the eddying of current in a blind, dilated

venous sac or pouch, or it might also be produced at points of constriction in the course of a dilated tortuous vein."⁶ This view is supported by the clinical features and necropsy findings of cases previously reported, and by the circumstances of the case here presented—the maximal intensity of the murmur and the thrill being at the site (Fig. 4B) where the currents of the four tortuous veins met. When no obvious subcutaneous varicosities are present, it is probable that necropsy would reveal the presence of varicosities not too deeply buried in the abdominal wall. Yater and Kenrick¹⁵ stated that if the murmur is merely the result of blood flow from small vessels into larger ones in or close to the abdominal wall, it is then not necessary to assume that patency of the umbilical vein exists. Bloom²⁶ also mentioned that even when all the necessary factors for the production of hum appear to be present (that is, portal hypertension and porto-systemic anastomosis with abdominal varicosities) no sound may be heard. Indeed, among the fifty-five cases reported by Armstrong *et al.*, seventeen of the patients showed patent umbilical or para-umbilical veins and had either a hum or a thrill, or both, but there were three who had a murmur but no patent vein was demonstrated whereas three others had a patent vein at necropsy but no hum could be elicited during life. Furthermore, it is quite common to meet with extreme hepatic cirrhosis in the absence of dilated channels in the falciform ligament and abdominal wall.

Other additional clinical criteria for the diagnosis of the Cruveilhier-Baumgarten syndrome are splenomegaly^{6,12} with or without hepatomegaly, eosinophilia,¹² anemia⁶ and persistent leukopenia.^{6,12,24} All these findings are present in our case. The persistent leukopenia is apparently on the basis of hypersplenism as demonstrated in our case by the strongly positive Doan's adrenalin test.³⁰

The pathogenesis of this disease apparently depends on two factors: a congenital and an acquired one. The umbilical vein must remain as a potentially patent structure after birth (analogous to the congenital theory of a weak or wide hiatal aperture in esophageal hiatus hernia). In addition, an acquired lesion anywhere along the portal vein, in the liver, or in the hepatic vein must be present. The most frequent lesion is, of course, cirrhosis of the liver, more than 90 per cent of the cases reported in the literature being attributable to that.

However, such other less frequently encountered conditions as hypoplasia or stenosis of the portal vein, thrombosis of hepatic or portal veins, cavernous transformation of the portal vein, etc., could conceivably give rise to a similar clinical picture. Such lesions, we believe, may well have existed in some of the reported cases in which cirrhosis was not found.

Treatment is medical. Caution is especially advised against surgical intervention in this type of case.³⁹ Splenectomy is of no value and particularly contraindicated because of the danger of hemorrhage from the greatly dilated venous channels in the abdominal wall.^{6,28,31,39} Havens and Gambill²⁸ cautioned against the increased danger of doing paracentesis, peritoneoscopy or biopsy of the liver in this condition. Successful results, however, were reported by Kennedy and Rousselot²⁴ and Santy *et al.*²⁷ after splenectomy and splenorenal anastomosis.

SUMMARY

A case of Cruveilhier-Baumgarten syndrome is presented, with a discussion of the important clinical features of this entity, which include a prominent para-umbilical vein, a venous hum and a thrill at the site of the para-umbilical circulation, splenomegaly with or without hepatomegaly, anemia, eosinophilia and persistent leukopenia. The pathogenesis of the disease is also briefly discussed.

The diagnosis depends on the physician's awareness of this entity and can usually be made by careful observation and auscultation of the abdomen when any disease resulting in portal hypertension, notably cirrhosis, is present.

We believe this is the first case of Cruveilhier-Baumgarten syndrome in which definitive confirmation by a glucose tolerance test of the portal anastomotic nature of a dilated abdominal vein was rendered.

The case here presented is probably another example—therefore the seventh in the literature—of Cruveilhier-Baumgarten *disease* (rather than *syndrome*) in view of the normal findings at liver biopsy and other criteria. However, since only necropsy affords definitive confirmation, we designate our case as Cruveilhier-Baumgarten syndrome, the eighty-sixth such case described in the literature.

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Pulmonary Fibrosis Due to Chronic Granulomatous Pneumonitis of Unknown Etiology*

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It is well recognized that pulmonary fibrosis is a common sequel to chronic or repeated pulmonary infection of all types, sarcoidosis, irradiation, infarction of the lungs and exposure to agents such as silica and beryllium.¹ Pulmonary fibrosis of unknown origin is a rare condition which is being recognized with increasing frequency both clinically and pathologically. The close similarity of some of these latter cases has warranted their being classified as the same disease entity. The classic example of this is the acute diffuse interstitial fibrosis of the lungs first described by Hamman and Rich² and subsequently by others,⁵⁻¹⁰ with some modification and extension of the original criteria. The type and degree of functional impairment that accompanies pulmonary fibrosis, regardless of the origin, seems to depend for the most part upon the pattern rather than the extent of fibrosis.^{3,4} The purpose of this paper is to report a patient presenting severe pulmonary fibrosis of undetermined etiology with progressive cardiopulmonary disability and death in whom extensive study was possible.

CASE REPORT

L. W. H., a thirty year old white farmer, was admitted to the Veterans Administration Hospital, McKinney, Texas, for the twelfth time on May 26, 1953. His present illness began in March, 1949, with the sudden onset of a severe, non-productive cough, frequently accompanied with nausea and vomiting. The cough progressed in severity and became productive of 1 to 2 ounces of clear mucoid sputum daily. There was a weight loss of 40 pounds in three months, but only slight loss of appetite. Exertional

dyspnea and weakness became so marked he was unable to continue work as a farmer. The sputum examinations for tubercle bacilli and tuberculin skin tests performed by his private physician were said to be negative. Following a chest x-ray at another institution he was advised that he probably had pulmonary tuberculosis. For this reason he was admitted for the first time on October 27, 1949. Upon admission he denied chest pain, hemoptysis, night sweats, wheezing respirations, previous pulmonary infections and exposure to sources of beryllium, silica or other unusual dusts. Other positive historical points included: occupation as a farmer with exposure to farm and fertilizer dusts; service in U. S. Navy from 1942 to 1948 with tours in the Southwest Pacific; "fever" while in New Guinea in 1944; gonorrhea in 1945; "mumps" in 1948; and occasional nocturia without dysuria. In the month prior to onset of symptoms he had assisted in razing a chicken house and an old home, being exposed to considerable dust each time. Acute respiratory symptoms on these occasions were denied. Physical examination revealed a thin, undernourished, young white male who appeared chronically ill. Blood pressure was 104/74 mm. Hg, pulse 80, temperature 98.6°F., and respirations 20. Tactile fremitus was increased over the right lower lung posteriorly but there were no rales. A 1.5 cm. pigmented nevus was present on the lower back and a few small axillary lymph nodes were palpable. Routine laboratory studies revealed: White blood count of 14,500, with 78 per cent neutrophils, 16 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils; hemoglobin 13.5 gm. per cent; corrected sedimentation rate of 28 mm. in one hour; normal

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urinalysis; and negative serologic test for syphilis. The hospital course was uneventful except for persistence of cough, dyspnea and weakness with occasional temperature elevations to 100°F. Repeated cultures of sputum and gastric washings for tubercle bacilli and fungi were negative. Skin tests for tuberculin (PPD), coccidioidin and aspergillin were negative, but histoplasmin (1:1000 diluent) gave a 1+ reaction. Serum total proteins were 7.9 gm. per cent, with albumin-globulin ratio of 1.3:1. The cephalin cholesterol flocculation test was 3+ and the thymol turbidity test 2 units. Histologic and bacteriologic examination of bone marrow and of lymph nodes taken from two sites failed to reveal abnormalities. Cytologic studies of bronchial washings were also negative. The vital capacity was 3.8 L. Admission chest x-ray (Fig. 1A) revealed extensive and diffuse pulmonary infiltrations with exudative and fibrotic components suggesting an acute granulomatous process. Prominence of the pulmonary artery segment was also present. Other x-ray studies, including bone survey, cardiac fluoroscopy and planigraphic studies for mediastinal and hilar nodes, were negative. Bronchoscopy was not helpful. Because of failure to establish a diagnosis, exploratory thoracotomy was performed and biopsy of the lung was taken. At the time of surgery nodular lesions of various sizes were found throughout the entire lung on inspection and palpation. There was no enlargement of mediastinal or hilar nodes. The histologic report on the sections through the granulomatous lesions was "chronic granulomatous pneumonia, etiology undetermined." (Fig. 2.) Therapy included prolonged courses of penicillin and aureomycin without change. A trial dose of x-ray therapy was given to a small area of one lung with subsequent slight clearing of the process. The patient, relatively unchanged, was discharged May 11, 1950.

For the next twelve months the patient got along fairly well without specific therapy but continued to have a non-productive cough, exertional dyspnea and easy fatigability. There were occasional temperature elevations to 100–101°F., and he seemed especially sensitive to dusts. Exposure to dust from the harvesting of hay on his farm was followed by acute respiratory symptoms and high fever. During this period he was admitted to the hospital on four occasions, twice for follow-up examinations and twice for x-ray therapy to the lungs. He received 2,400 r

to the right lung in August, 1950, and 2,600 r to the left lung in December of the same year. It was thought that each lung showed some clearing of the infiltrate after receiving x-ray therapy but this was temporary and the patient noted little subjective change. Sputum studies again were negative for tubercle bacilli and fungi.

The sixth admission was on June 16, 1951, because of right pneumothorax with 30 per cent collapse. This subsequently increased, requiring closed thoracotomy because of increasing respiratory embarrassment. He was discharged on August 17, 1951, with a 10 per cent residual right pneumothorax which persisted until about May, 1952. A small apical pneumothorax was noted on the left on two occasions but did not require specific therapy.

He was again admitted August 21, 1951, because of sudden onset of severe pain in the right costovertebral angle radiating into the right flank and right lower quadrant of the abdomen. This was followed in several hours by a hard shaking chill and fever to 104°F. Flat plate and KUB films revealed no abnormalities. Several urinalyses showed only a few white blood cells in the sediment and cultures were negative. Repeated blood cultures, including specific efforts to culture brucella, were also negative. Agglutination studies were normal. Bone survey films again revealed no abnormalities. Skin tests were repeated and again were negative, except for a 3+ reaction to 1:1000 histoplasmin. A right supraclavicular lymph node biopsy was also negative.

The temperature returned to normal on the day of admission and remained normal, with the pain subsiding entirely by the third hospital day. Because of some progression of his pulmonary disease by x-ray, and the slow, downhill course clinically, it was decided to give a trial course of ACTH. Beginning September 28, 1951, 10 mg. was given intravenously daily for seven days. The drug was stopped because of development of edema, and a diuresis with a 9 pound weight loss followed. The course of his disease was not significantly altered and he was discharged on October 12, 1951.

The patient returned for his eighth hospital admission on November 21, 1951, with symptoms unchanged except for increase in exertional dyspnea. Laboratory studies including liver and renal function tests were all within normal limits, except for 19 per cent retention of bromsulfalein dye. The electrocardiogram was compatible

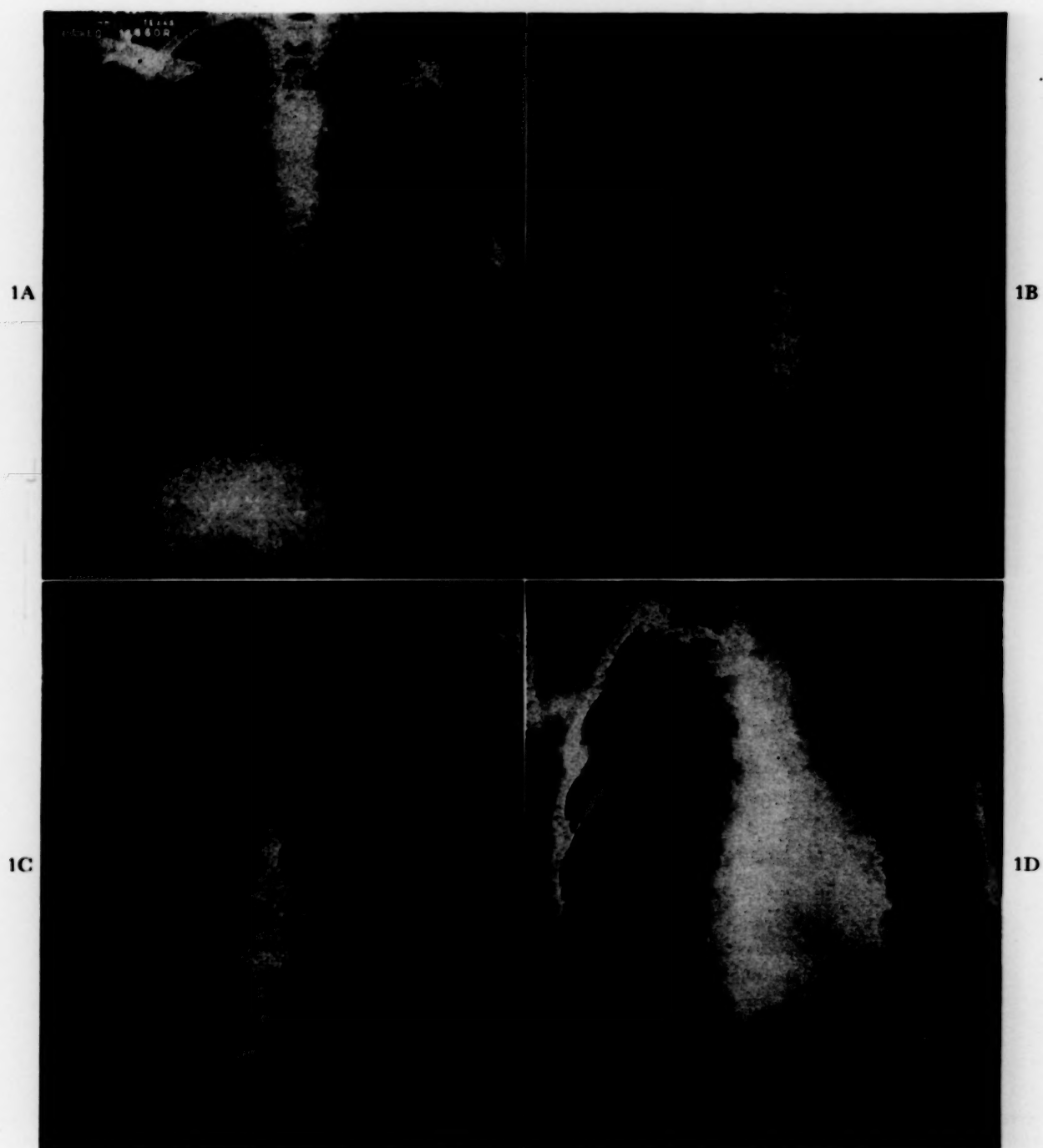


FIG. 1. A, October 28, 1949. Admission film showing diffuse pulmonary infiltrations and prominence of pulmonary artery segment. B, July 12, 1950. Film showing progression of disease in the right lung. The prominent pulmonary artery segment is again noted. C, January 20, 1952. Following ACTH and cortisone therapy. No significant change. Note that bullous changes have occurred and there is a pneumothorax on the left. D, February 9, 1953. Film taken approximately four months prior to death and after heart failure had supervened. The cystic changes in the lungs have become more marked and there is cardiomegaly.

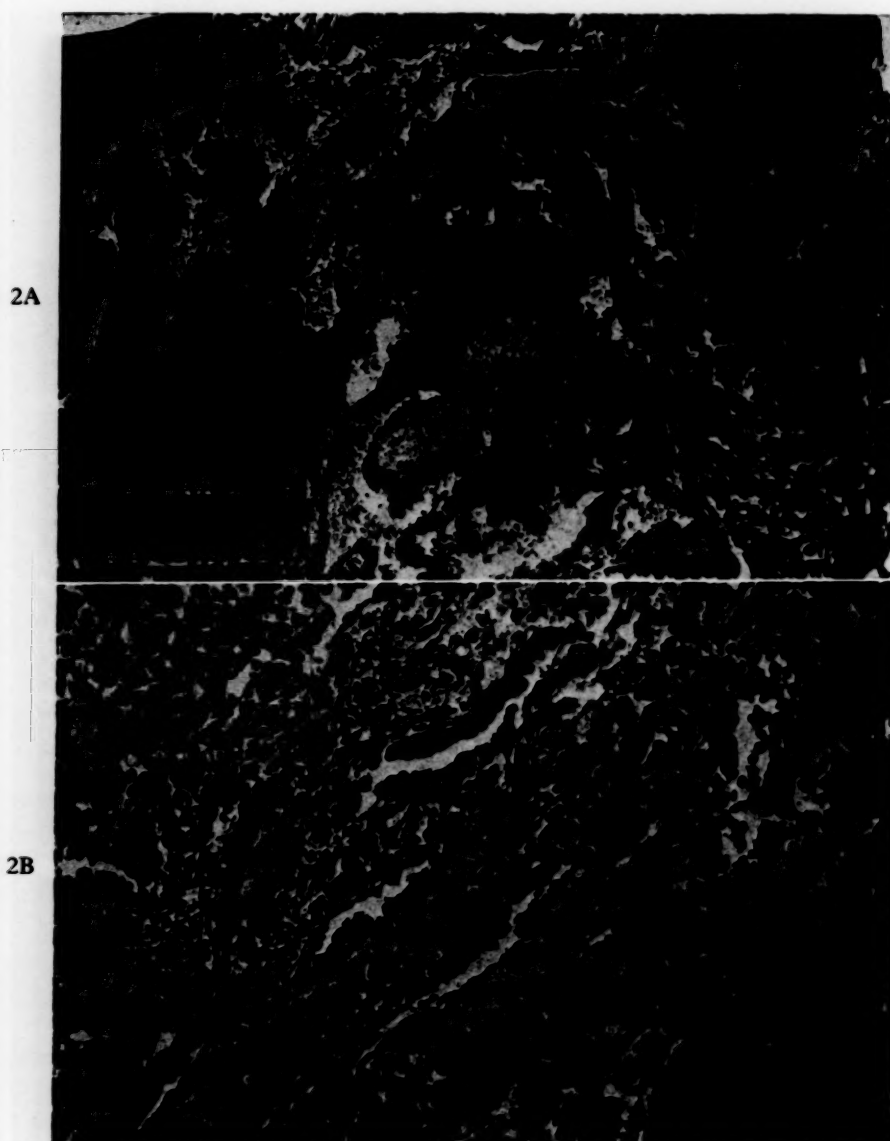


FIG. 2. Photomicrographs of the lung biopsy. A, low magnification showing areas of necrosis, fibrosis and marked inflammatory reaction; $\times 50$. B, higher magnification reveals numerous macrophages with foamy cytoplasm, scattered lymphocytes, neutrophils and eosinophils in interstitial tissue and alveoli. Some of the air spaces are lined by cuboidal epithelium; $\times 290$.

with early cor pulmonale. On November 23, 1951, pulmonary function studies, including arterial blood gas determinations, were obtained prior to cortisone therapy. These results are recorded in Tables I and II and were interpreted as showing severe restriction of ventilation with evidence of rather marked disturbance in alveolar-capillary diffusion of oxygen. Cortisone was begun intramuscularly on December 7, 1951, and continued until December 26, 1951, for a total of 3,025 mg. There was an excellent drop in the circulating eosinophils, but on the fourteenth day of therapy clinical signs of

bilateral pneumonia developed, evidenced by rales and spiking fever. Even though the chest x-ray (Fig. 1C) showed no significant change, these signs cleared slowly after five weeks of vigorous antibiotic therapy and other supportive measures, including intermittent oxygen. Three weeks after the onset of the pneumonia a 20 per cent pneumothorax developed on the left but responded to conservative measures. Pulmonary function studies which had been repeated immediately after cortisone revealed no significant changes. (Tables I and II.) The patient lost 23 pounds in weight and when discharged on

February 21, 1952, his general condition was slightly more deteriorated than on admission.

He was seen March 20, 1952, because of increase in cough, dyspnea and fever for ten days. Treatment with antibiotics and aerosol bronchodilators was accompanied by consider-

severe, bilateral, pleuritic chest pain. Physical examination revealed no essential change except for cyanosis, increased rales in both lungs and dyspnea at rest. The chest film again showed no change. Shortly after admission the patient went into congestive heart failure. This was

TABLE I
VENTILATORY FUNCTION STUDIES

Ventilation L/Min/	Before Treatment 11-23-51	After Treatment 12-27-51	Predicted Values
Ventilation L/Min/M ²	5.8 L	5.6 L	< 4.0 L
O ₂ Consumption cc/Min/M ²	174 cc	173 cc	130 ± 25 cc
O ₂ Removal Rate cc/L.Vent.	30 cc	31 cc	30 - 40 cc
Inspiratory Capacity	1.6 L	1.5 L	3.45 L
Expiratory Reserve Volume	525 cc	395 cc	1.0 L
Expiratory (EVC) Vital Capacity	1.87 L (42%)	1.78 L (40%)	4.45 L
One Second (IVC) Vital Capacity	990 cc (27%)	950 cc (26%)	3.65 L
$\frac{I.VC}{EVC} \times 100$	53%	53%	> 82%
Residual (RV) Volume	3250	—	1675 cc
Total (TC) Capacity	6150	—	5560 cc
$\frac{RV}{TC} \times 100$	53%	—	< 25%
Maximum Breathing Capacity	66 L (37%)	59 (33%)	180 L

able symptomatic improvement. X-ray and laboratory studies did not show significant changes, and the electrocardiogram was interpreted as showing more evidence of cor pulmonale.

On follow-up examination July 28, 1952, some decrease in cough and sputum was noted but the chest x-ray was essentially unchanged in appearance.

The next period of hospitalization, from September 23, 1952, to January 26, 1953, was precipitated by increase in dyspnea, weakness, nausea and vomiting, and the appearance of

further complicated by left pneumothorax requiring closed thoracotomy and shortly thereafter a small right pneumothorax. Because of continued bilateral pleuritic chest pain it was necessary to give narcotics frequently. During this admission CO₂ retention occurred for the first time and cylindruria was noted. Complement fixation studies for histoplasmosis were negative. * Complement fixation for coccidioides was reported as positive in a serum dilution of

* Courtesy of Dr. M. L. Furcolow, U. S. P. H. S., Univ. of Kansas Medical Center, Kansas City, Kansas.

1:2 but precipitin tests were negative; these are equivocal findings.*

The problem now was one in management of chronic congestive failure, marked chest pain and poor nutrition. In spite of his generally poor condition, at his request he was allowed to

pleural spaces and 150 cc. in the pericardial sac.

The right lung weighed 875 gm.; the left, 500. Both were firm, distended, hypocreptant and covered with moderately thickened, opaque pleura. Small subpleural blebs were over all sur-

TABLE II
BLOOD STUDIES

	Before Treatment 11-23-51			After Treatment 12-27-51			Predicted Values
	Resting Room Air	Exercise Room Air	After 25 Min. 100% O ₂	Resting Room Air	Exercise Room Air	After 25 Min. 100% O ₂	
CO ₂ Content Vol. %	48	47	49	54	51	51	< 50 Vol. %
pCO ₂ mmHg	34	33	38	—	—	—	< 40 mmHg
pH	7.45	7.45	7.50	—	—	—	7.36 - 7.46
O ₂ Saturation	78%	70%	92%	86%	77%	92%	< 96%
pO ₂ mmHg	44	32	—	—	—	—	> 90 mmHg
Effective Alv. pO ₂ mmHg	102	115	—	—	—	—	> 100 mmHg
Alveolar - Arterial pO ₂ Gradient	58	84	—	—	—	—	< 15 mmHg
O ₂ Consumption cc/Min M ²	155 cc	435 cc	174 cc	186 cc	462 cc	173 cc	—
Hematocrit	45%	—	45%	48%	—	47%	—

return home on January 26, 1953, to the care of his private physician.

On February 7, 1953, he was readmitted because of progressive failure with anasarca, severe pain and marked nausea and vomiting. Chest x-ray at this time revealed again the widespread infiltrations with localized areas of emphysema and cystic changes, with increased prominence of the pulmonary artery segment and marked, generalized cardiac enlargement. He responded somewhat to salt restriction and mercurials. The patient returned again for his twelfth and final admission on May 26, 1953, with marked anasarca, cyanosis and venous pressure of 435 mm. H₂O. His failure was refractory to all forms of therapy and death occurred quietly on July 2, 1953. During this final hospitalization there was marked cardiac rhythm disturbance, CO₂ retention, depression of serum proteins and hypopotassemia.

Autopsy was started one hour after death. The body was poorly nourished and the subcutaneous tissue was decreased. Three thousand five hundred cc. of straw-colored fluid were in the peritoneal cavity, 200 and 150 cc. in the

faces of the lungs and were more numerous in the apices. There was increased resistance to sectioning. The cut surfaces were mottled and throughout all sections was a network of slender bands of depressed gray tissue and cysts with a smooth, gray, glistening lining, measuring 0.2 to 2 cm. The bronchi could be traced, except for fine radicles, and were not remarkable. There was moderate arteriosclerosis. The hilar lymph nodes were not unusually enlarged.

The heart weighed 280 gm. The right ventricle was 5 to 6 mm. in thickness, the left 10 mm. The right heart was dilated and the tricuspid ring was 14 cm. in circumference. No endocardial or myocardial changes were noted. The abdominal viscera and the brain were not remarkable.

Microscopically, diffuse severe interstitial fibrosis and small cystic spaces were present in all sections. (Fig. 3.) In some areas lung tissue was completely replaced by dense fibrous tissue. Bronchioles were occasionally compressed by surrounding fibrosis. A few contained fibrous tissue within the lumina. The cysts were either unlined or were lined by low cuboidal or columnar epithelium. Small loose collections of lymphocytes, a few plasma cells and eosinophils were noted and a few similar cells were scattered

* Courtesy of Dr. C. L. Smith, Univ. of California School of Public Health, Berkeley, California.

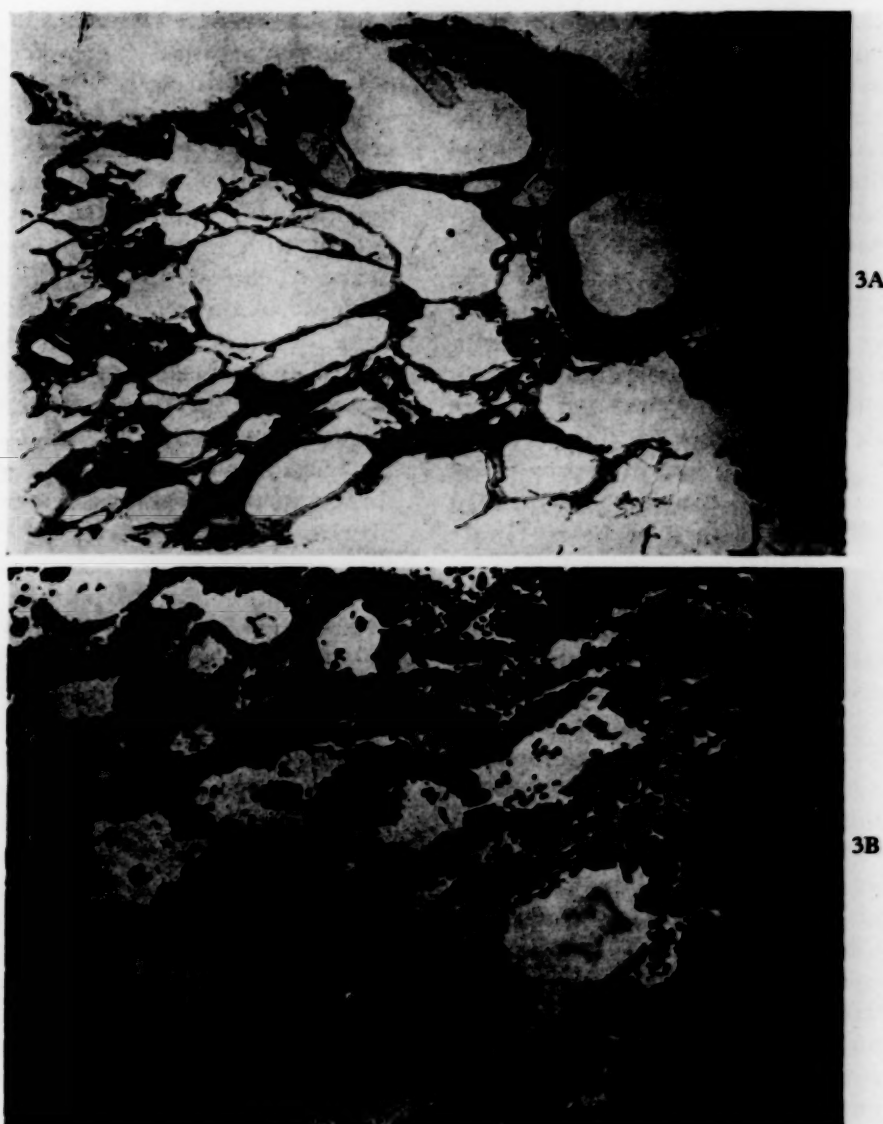


FIG. 3. Photomicrographs of lung sections at autopsy. A, a representative section of the lungs showing emphysema, fibrosis, prominent bronchioles, arteriosclerosis and lack of inflammatory cells; $\times 8$. B, higher magnification of one of the rare areas of fibrosis in which lymphocytes, histiocytes and a few eosinophils were noted; $\times 80$.

in the fibrous tissue. There was arteriosclerosis of larger arteries and subintimal fibrosis of smaller ones. The arterioles and capillaries were not remarkable. The etiology of pulmonary disease was not evident. Sections of other organs revealed central lobular atrophy of the liver, visceral hyperemia and minute perivascular hemorrhages in the brain-stem.

The lungs at autopsy, showing principally a severe fibrosis, differed markedly from the lung biopsy done three years before death. (Figs. 2 and 3.) At that time the lesion was predominantly a chronic granulomatous process. Some of the granulomas had central necrosis sur-

rounded by histiocytes, lymphocytes, plasma cells and polymorphonuclear leukocytes. Similar cells were diffusely scattered about bronchioles and in the interstitial tissue. Many alveoli contained macrophages and fibrin. There was fibrosis but it was much less extensive than at autopsy. A vascular lesion was not observed except for moderate, subintimal fibrosis of small arteries such as may be seen in any chronic pneumonitis.

COMMENTS

There are several unusual features of this case which tend to set it apart from others, and

therefore require further discussion. The onset was abrupt, without preceding respiratory illness, but the clinical course was characterized by chronicity and exceeded four years in duration. The patients with diffuse interstitial pulmonary fibrosis of Hamman and Rich^{2,5} characteristically had rapid onset of symptoms following a recent acute respiratory illness, and the disease usually ran its course to death within a few weeks or months. In some cases reported in the last five years⁷⁻¹⁰ the duration of symptoms was from eighteen to thirty-six months prior to death. The terminal picture was one of severe cor pulmonale and pulmonary insufficiency. This is not unusual in severe progressive pulmonary fibrosis but patients may present themselves with the picture of heart failure predominating, thus obscuring recognition of the underlying pulmonary disease process.

Pulmonary function studies two and one-half years after onset of the disease revealed decrease in lung volume, restricted ventilation and impairment of alveolar-capillary diffusion. It is believed that decrease in lung volume and restriction of ventilation occurred first as a result of the "stiffening" of the lung parenchyma. As the disease process continued there was increasing fibrosis, organization of exudate, destruction of alveoli and obliteration and obstruction of bronchioles. Thus the pulmonary vascular bed was greatly reduced and alveolar ventilation diminished, resulting in elevation of pulmonary arterial pressure and in impairment of oxygen transfer across the alveolar membrane. Later in course CO₂ retention became evident, suggesting further disturbance in alveolar ventilation. Impairment of alveolar-capillary diffusion in pulmonary fibrosis has been noted by others.^{11,12} Specific therapeutic efforts aimed at altering the basic disease process met with failure. Deep x-ray therapy to both lungs was followed by slight, transient clearing of the infiltrations without change in the clinical state. One might speculate on the possibility of this therapy increasing the fibrosis subsequently. ACTH and cortisone did not alter the course of the disease except to precipitate an exacerbation of the ever present chronic pulmonary infection. These drugs have been used with beneficial effect in some cases¹⁰ of diffuse interstitial pulmonary fibrosis and in a number of patients with other diseases in which pulmonary fibrosis plays a major part^{11,12} even though they usually afford only palliative or symptomatic therapy in most

instances. Perhaps the use of these drugs earlier in the course of this case would have produced more beneficial results.

The pathologic process in the lungs during the first year of his clinical illness was demonstrated by lung biopsy to be chronic granulomatous pneumonia. It appears that only in an occasional patient with progressive pulmonary fibrosis of unknown etiology has the opportunity to obtain a biopsy of the lung been afforded.¹⁰ Thus in most instances, study of the pulmonary histopathology has been accomplished at postmortem examination and probably represents the end stages of the process. The microscopic picture of the lungs at autopsy in the present case is quite similar to that of diffuse interstitial pulmonary fibrosis. Another interesting feature in the present case was the limitation of the disease process entirely to the pulmonary parenchyma without involvement of the reticulo-endothelial or other systems. All other pathologic changes observed at autopsy could be attributed directly or indirectly to the primary process in the lungs. Repeated lymph node biopsies made during life and extensive histologic examination of other tissues at autopsy failed to reveal abnormalities. This is frequently the case in diffuse interstitial pulmonary fibrosis but not so in other diseases causing or accompanied by pulmonary fibrosis.

The etiology of the disease in this case was not determined. Exhaustive and repeated studies failed to reveal the presence of fungi or tubercle bacilli, either by culture or in tissues. Tissue cultures of lymph nodes and lung tissue, both ante- and postmortem, were negative. Routine sputum cultures revealed varying organisms from time to time consistent with normal flora or low-grade chronic infection of the tracheo-bronchial tree. Histoplasmosis was considered a likely possibility, in view of the history of the patient dismantling a chicken coop shortly before the onset of the illness, and the consistently positive skin reactions to histoplasmin. Also the histologic picture of the lungs at the time of biopsy did resemble to some extent the lesions seen in pulmonary histoplasmosis produced experimentally in animals. However, serologic studies were not helpful and, most important of all, the organism was never demonstrated or isolated. Schiff's periodic acid stains on the biopsy and autopsy specimens were negative. Histologically, there was some resemblance to beryllium granuloma at the time of lung biopsy. However, the evidence of

beryllosis was sparse. Sarcoidosis should be mentioned but the strict limitation of the disease to the lungs would seem to exclude this as a possibility and the histologic picture was not at all characteristic. One must also consider the interesting possibility that interstitial fibrosis of the lungs may begin as a granulomatous pneumonia.

SUMMARY

A case of severe pulmonary fibrosis with progressive impairment of cardiopulmonary function resulting from chronic granulomatous pneumonia of unknown etiology is presented. The salient features, including the clinical course, cardiopulmonary function and attempts at therapy are discussed.

It is suggested that, in the absence of antemortem lung biopsy, this case would have been classified as a modified form of diffuse interstitial pulmonary fibrosis as described by Hamman and Rich.²

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Whipple's Intestinal Lipodystrophy*

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IN 1907 Whipple¹ reported the clinical and autopsy findings in the case of a thirty-six year old physician whose protracted illness had been characterized by a gradual loss in weight and strength, steatorrhea, anemia, indefinite abdominal signs, polyarthritis and chronic cough. The striking anatomic findings were those of massive deposition of neutral fat and fatty acids in the intestinal and mesenteric lymphatic tissues, infiltration of the submucosa of the intestine by large mononuclear cells and the absence of chylous obstruction. In his report, which is destined to become an American medical classic, Whipple proposed that the syndrome be termed intestinal lipodystrophy. Dr. William S. Thayer, who had been the patient's physician, commented "As one looks back upon the history of this case in connection with the remarkable observations at autopsy, it is difficult to resist the conclusion that we are here dealing with a definite and hitherto unrecognized clinical picture with which we shall meet again."

The disease has been "met with again" on rare occasions since the original report, and to date approximately forty-two cases have been reported. In addition, several excellent reviews²⁻⁵ have appeared, especially that of Hendrix et al.² which added five new cases, two of which were diagnosed during life by mesenteric lymph node biopsy. Since then Jones⁶ has reported the occurrence of the disease in a woman, presumably the first to be reported, if the criteria of Hendrix et al.² are to be accepted. In fact, there may even be a question regarding this case, for the operative note speaks of distended lacteals suggesting chylous obstruction. Of further interest in this case is the history of sustained remission apparently following the use of ACTH and cortisone.

The rarity of Whipple's disease prompts the report of the present case which was correctly

diagnosed on clinical grounds and subsequently confirmed by exploratory laparotomy and biopsy of the mesenteric lymph nodes.

CASE REPORT

This fifty-six year old married French baker was admitted to the Presbyterian Hospital in New York City on October, 1952, with the chief complaint of weight loss and diarrhea which began ten weeks previously while on a trip in France. His illness began suddenly without known prodromata, with four to six copious, fluid, foul, light yellow stools containing no gross blood or mucus. Anorexia and periumbilical discomfort without cramps then developed. Paregoric seemed to help. One week later drenching night sweats with fever ranging between 100-101°F. and an occasional chilly sensation developed. The patient began to lose weight and in ten weeks lost 25 pounds. He also noted tan pigmentation of his face and complained of fatigability. Since 1918 he had had a mild non-productive chronic cough. There was a history of gonorrhea at twenty years, and of right renal colic with the passing of a stone in 1935. In 1942 he had undergone hemorrhoidectomy. No mineral oil had been taken for ten years although for several years before the hemorrhoidectomy he had taken one tablespoonful of mineral oil two or three times weekly. In 1948 he noted the acute onset of migratory polyarthritis lasting two or three days, clearing spontaneously without deformity and recurring at one- to three-week intervals. His physician thought these were bouts of palindromic rheumatism. There had been no joint pains for the preceding five months.

The general physical examination revealed an alert but chronically ill fifty-six year old man whose skin appeared tanned. There was evidence of recent weight loss but nothing else of significance was discovered on physical examination.

The pertinent laboratory data are recorded

* From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y. Presented at the alumni reunion of the University of Rochester School of Medicine, Rochester, New York, October 23, 1953.

in Table 1. The chief laboratory findings were those of steatorrhea as manifested by the stool content of numerous fatty acid crystals on microscopic examination, no detectable serum carotene and a low serum vitamin A level. It has been our experience in this clinic⁷ that

TABLE 1
LABORATORY DATA

Erythrocyte sedimentation	
rate	105 mm. in 1 hr.
Hemoglobin	9.5 gm./100 cc.
Red blood count	3.12 million per cu. mm.
Hematocrit	31 per cent
Serum cholesterol	102 mg. per 100 cc.
Serum cholesterol esters	63 mg. per 100 cc.
Oral glucose tolerance test:	
Fasting blood sugar	88 mg. %
½ hr.	94 mg. %
1 hr.	98 mg. %
2 hr.	89 mg. %
3 hr.	91 mg. %
Intravenous glucose tolerance	
test	Normal
Stool guaiac	Intermittently 1 plus to 4 plus, at times negative
Stool microscopic fat	4 plus fatty acid crystals
Serum carotene	0
Serum vitamin A level	62 units/100 cc.
Small intestine x-ray study	Disturbed motor physiology without demonstrable organic disease

absence of carotene from the serum is usually indicative of a serious defect in fat absorption. With the finding of a flat oral glucose tolerance curve, and a normal intravenous glucose curve, the question of non-tropical sprue was raised. The chief objections to this diagnosis were the markedly elevated erythrocyte sedimentation rate of 105 mm. in one hour, and the febrile course. We have never seen this degree of elevation of the sedimentation rate in uncomplicated primary sprue in this clinic.⁸

In view of these findings and the unusual clinical history, the diagnosis of Whipple's intestinal lipodystrophy was proposed. A two-week course of intensive anti-sprue therapy failed to influence the patient's condition. He therefore underwent laparotomy on November 12, 1952, under general anesthesia. The operative findings were those of classic Whipple's disease manifested by mesenteric lymphadenopathy with individual nodes varying from 1 to 6 cm. in diameter. Two nodes were excised for study. The spleen was slightly enlarged, hard, and had numerous firm perisplenic adhesions. The pancreas, liver and stomach appeared normal. The jejunal wall appeared somewhat

thickened and exhibited streaked white mottling. There was no evidence of chylous obstruction.

The pathologist's report was as follows: "Gross findings: The specimen consists of a mesenteric lymph node of the small intestine measuring 4 × 3 × 2.3 cm. It is surrounded by a few adhesions. On cut section it is yellowish, and a milky exudate is seen. In the milky exudate a certain number of very small fat droplets are seen.

"Microscopic findings: Sections of the lymph node (Fig. 1) show that a normal structure is altered by the presence of large numbers of vacuoles which vary greatly in size. Some of them could be called small cysts. The smaller ones are associated with phagocytes, some of which are multinucleated. In addition, some of the multinucleated giant cells contain fatty acid crystal clefts. Besides the vacuolated histiocytes there are also large collections of histiocytes which are finely granular, or which contain an amorphous basophilic substance. Most of the lymphoid tissue has been replaced by this peculiar lipid granuloma. Scharlach-R stain is strongly positive for all vacuoles described above.

"The findings here are consistent with those described by Hendrix and others as characteristic for Whipple's intestinal lipodystrophy.

"Additional note: PAS (Periodic-Acid-Schiff) positive¹² material present in the histiocytes."*

On November 26, 1952, because of failure to respond to supportive measures, the patient was started on a regimen of oral cortisone, 0.050 gm., four times a day. He improved gradually and was discharged in remission on December 24, 1952, with the advice to continue with cortisone, 0.050 gm., three times a day, multivitamin therapy by mouth, folic acid, potassium chloride and tincture of opium. He remained well for approximately two to three weeks, then relapsed despite these measures, and increasing diarrhea, weakness and weight loss developed. Readmission on January 20, 1953, was therefore necessary. During this admission he received 25 mg. of ACTH intramuscularly, every six hours, and cortisone was stopped; the previous supportive and symptomatic measures including bantnine were continued. In addition, he was given sorlate® and pancreatic extract. However, he continued to do poorly and on February 3, 1953, bronchopneumonia developed. Type 23 pneu-

* The author is indebted to Dr. Raffaele Lattes of the Department of Surgical Pathology for his report as well as for his generous assistance in the study of this case.

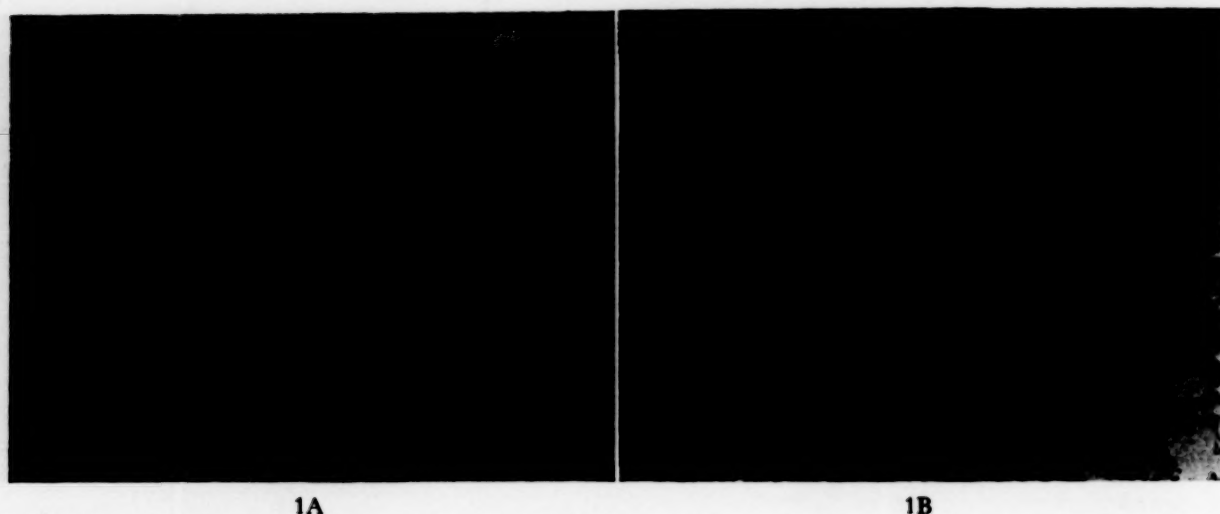


FIG. 1. A, low power photomicrograph of two lymph node fragments showing characteristic sieve-like appearance due to presence of innumerable vacuoles scattered in lymphoid tissue. B, medium power photomicrograph showing vacuoles of different sizes associated with multinucleated giant cells of foreign body type, mononuclear histiocytes and moderate fibrosis. The vacuoles stain strongly with Scharlach-R.

cocci were recovered in pure culture from his sputum. At this time paralytic ileus also developed which cleared when banthine and tincture of opium were discontinued. In view of a falling hematocrit (24 per cent), positive stool guaiac test and hypoalbuminemia (2.6 gm. per 100 cc.), multiple transfusions of whole blood were given to a total of 3,500 cc., from February 4 to February 22, 1953. He was also given penicillin intramuscularly in full dosage. With these measures his disease remitted and on February 26th ACTH was stopped and cortisone, 50 mg., was administered 4 i.d. At the time of discharge on March 6, 1953, he was feeling better, eating very well, gaining strength and free of diarrhea. Of all the medications given to him for diarrhea, tincture of opium seemed by far the most effective. He was seen at regular intervals as an outpatient, and remained on a regimen of tincture of opium b.i.d., sorlate 1.0 gm. t.i.d., potassium chloride 0.3 gm. 4 i.d., pancreatin powder, 1 teaspoonful t.i.d., folic acid, 0.005 gm. t.i.d., and a multivitamin supplement. His dose of cortisone was decreased to 0.050 gm. t.i.d. His remission continued, except for several mild episodes of diarrhea, until May 25, 1953, when despite all therapeutic measures a severe relapse developed with uncontrollable diarrhea, fever, weakness, anorexia, vomiting and weight loss of 12 pounds in ten days. The dose of cortisone was increased to 0.050 gm. 4 i.d., then 6 i.d., to no avail. It was therefore, necessary to readmit him to the hospital on May 28, 1953. At this time it was decided

to try hydrocortisone (free alcohol) in the dosage of 5 mg. q. 4 h. by mouth.

Within twenty-four hours a dramatic remission appeared as manifested chiefly by rapid cessation of diarrhea, a return of strength and appetite, and sense of well-being. He rapidly regained his weight and within a week said he was feeling better than he had at any time since the onset of his original illness. He was discharged on June 13, 1953, and has been seen regularly as an outpatient, with maintenance doses of hydrocortone. Except for arthritic pain, he has remained in remission to date. In August, 1953, because of a scarcity of materials, it was necessary to change to hydrocortisone acetate which he still takes in the dose of 5 mg. 4 i.d., in addition to the other supportive measures described.

COMMENT

Whipple's intestinal lipodystrophy is a progressive disease of undetermined etiology for which no specific treatment is available. Recently reports have appeared on the beneficial effects of ACTH and cortisone in this disease.^{6,13,14} Our patient had a remission following cortisone therapy only to relapse while still taking it. His improvement while on ACTH is difficult to ascribe to this agent alone because of the many supportive and therapeutic measures necessitated by his grave illness. The second relapse while on cortisone apparently responded dramatically to hydrocortisone (free alcohol) in the dosage of 0.005 gm., q. 4 h. after ten times

the dose of cortisone had failed to influence his downhill course. It is difficult to judge the effectiveness of any new therapeutic measure in this variable disease but the response appeared to be dramatic and warrants further study of this agent.

The nature of the absorptive defect in Whipple's disease remains obscure for it does not appear to be due to mechanical obstruction of the lacteals and mesenteric lymphatics. It is suspected that a metabolic block of some sort interferes with the absorption of many substances from the intestinal lumen. It is now known that ACTH and cortisone, and probably hydrocortone, may improve absorption from the small intestine in sprue,⁹⁻¹¹ and it is because of these findings that these agents were employed in this patient. Unfortunately, we were unable to study the absorption of various substances from the intestine in this patient by balance technics. However, it can be stated on the basis of clinical observation that with the possible exception of hydrocortisone this patient failed to respond to these agents as strikingly as our patients with sprue. The defect in absorption is probably different in Whipple's disease.

Studies of pancreatic ferments in Whipple's disease have failed to reveal any gross deficiency² but at postmortem examination chronic pancreatitis of a mild grade has not been unusual. The role played by the digestive ferments of the succus entericus in health and disease has not been quantitatively evaluated in man. One wonders whether in Whipple's disease there might not be a failure of the small intestine to produce adequate quantities of the digestive ferments. Were this the case, despite normal pancreatic ferment production, there might still be a deficiency of intestinal enzymes. This might constitute the basis for further study. With this rather tenuous hypothesis it was decided to add full dosage of pancreatin, triple strength, three to four times daily, to the therapeutic plan. In addition, for sometime prior to this the patient had been taking sorlate, 1.0 gm., t.i.d. With these agents it was hoped to improve emulsification of fat in the intestine and perhaps thereby to facilitate its absorption. Whether this will in any way influence the course of this man's illness remains to be seen. He has relapsed twice despite these measures and it is evident that digestive enzyme deficiencies are not the primary difficulties although they may possibly contribute to his ailment.

The anemia seen in Whipple's disease has usually been ascribed to malnutrition, vitamin deficiency, steatorrhea or iron deficiency. However, in most of the reported cases blood has been present in the stool, at times explained by minute ulcerations in the gastrointestinal tract, at times unexplained.² In our patient no definite site of gastrointestinal bleeding was demonstrated by radiographic study or sigmoidoscopy, nevertheless it is apparent that his anemia was to a large degree due to chronic blood loss from the gastrointestinal tract, perhaps from pin-point ulceration.

SUMMARY

A case of Whipple's intestinal lipodystrophy occurring in a fifty-six year old man was diagnosed clinically, and confirmed by laparotomy and mesenteric lymph node biopsy. Approximately one year after the diagnosis was established the patient remains in remission apparently induced by hydrocortisone.

Acknowledgment: I am deeply indebted to Merck and Company for generous supplies of cortone and hydrocortone, and to Armour and Company for their generosity in supplying ACTH for this study.

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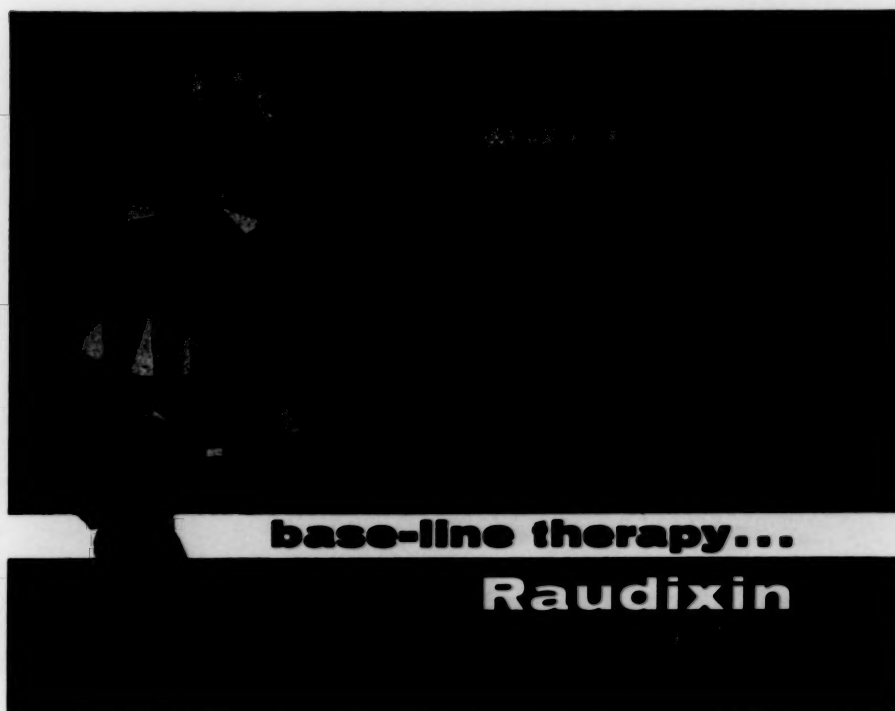
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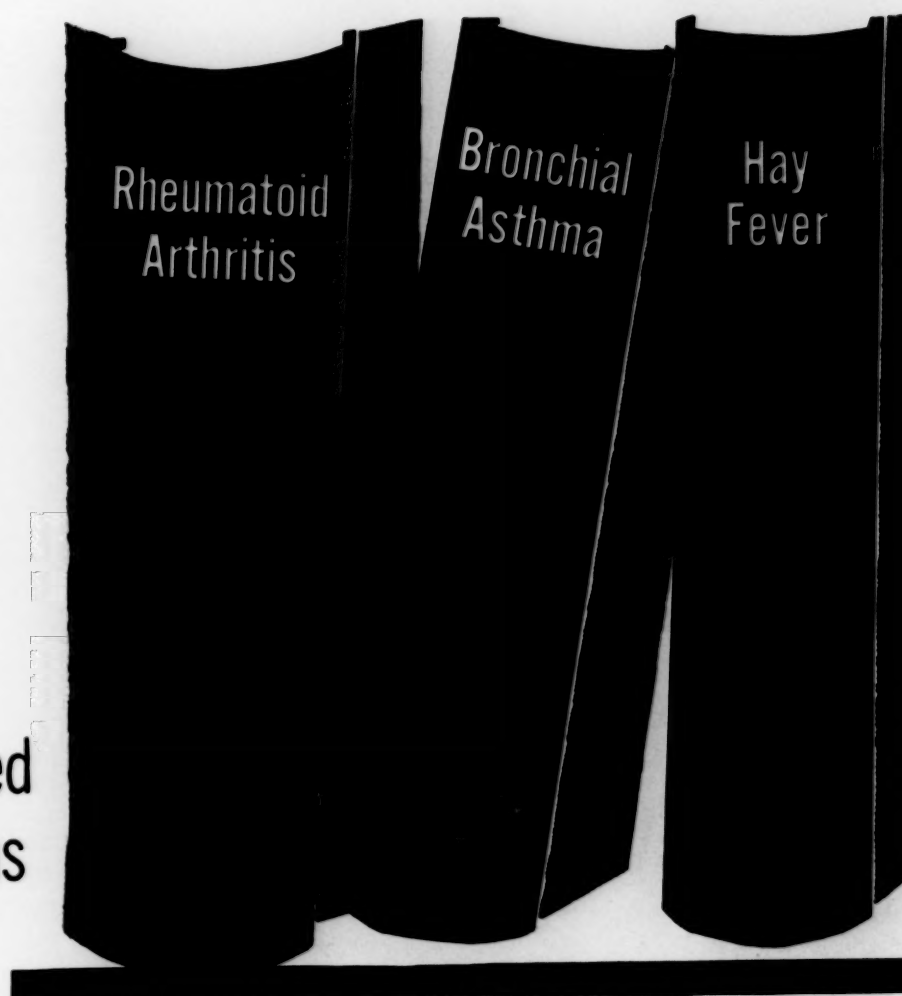
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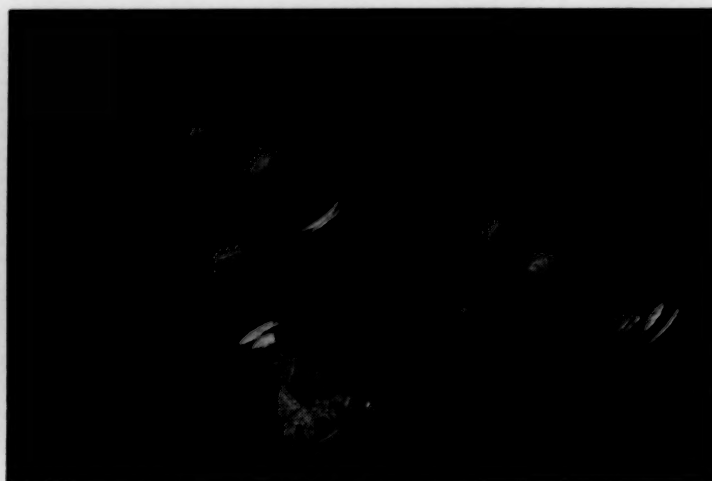
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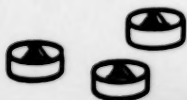
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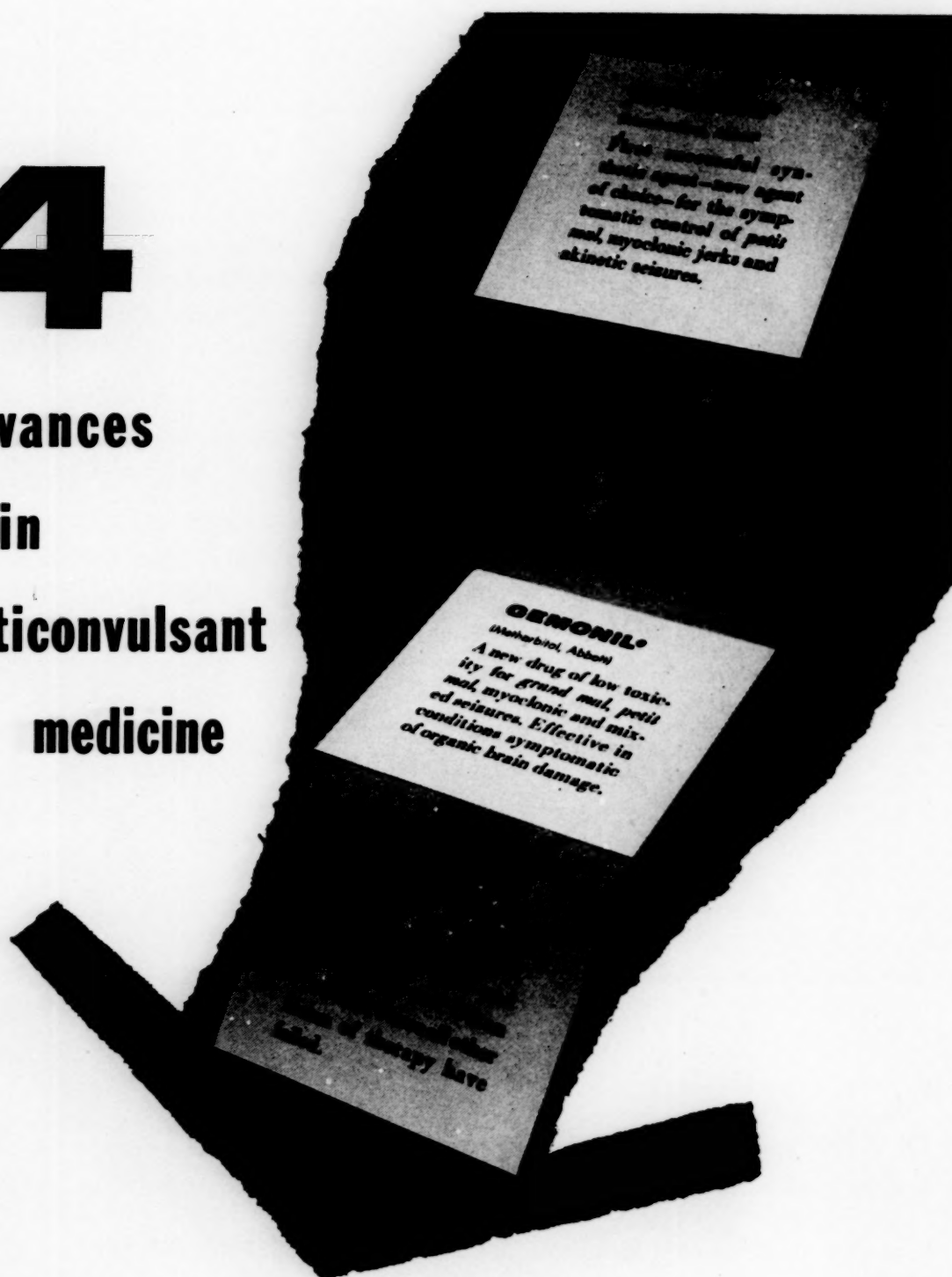
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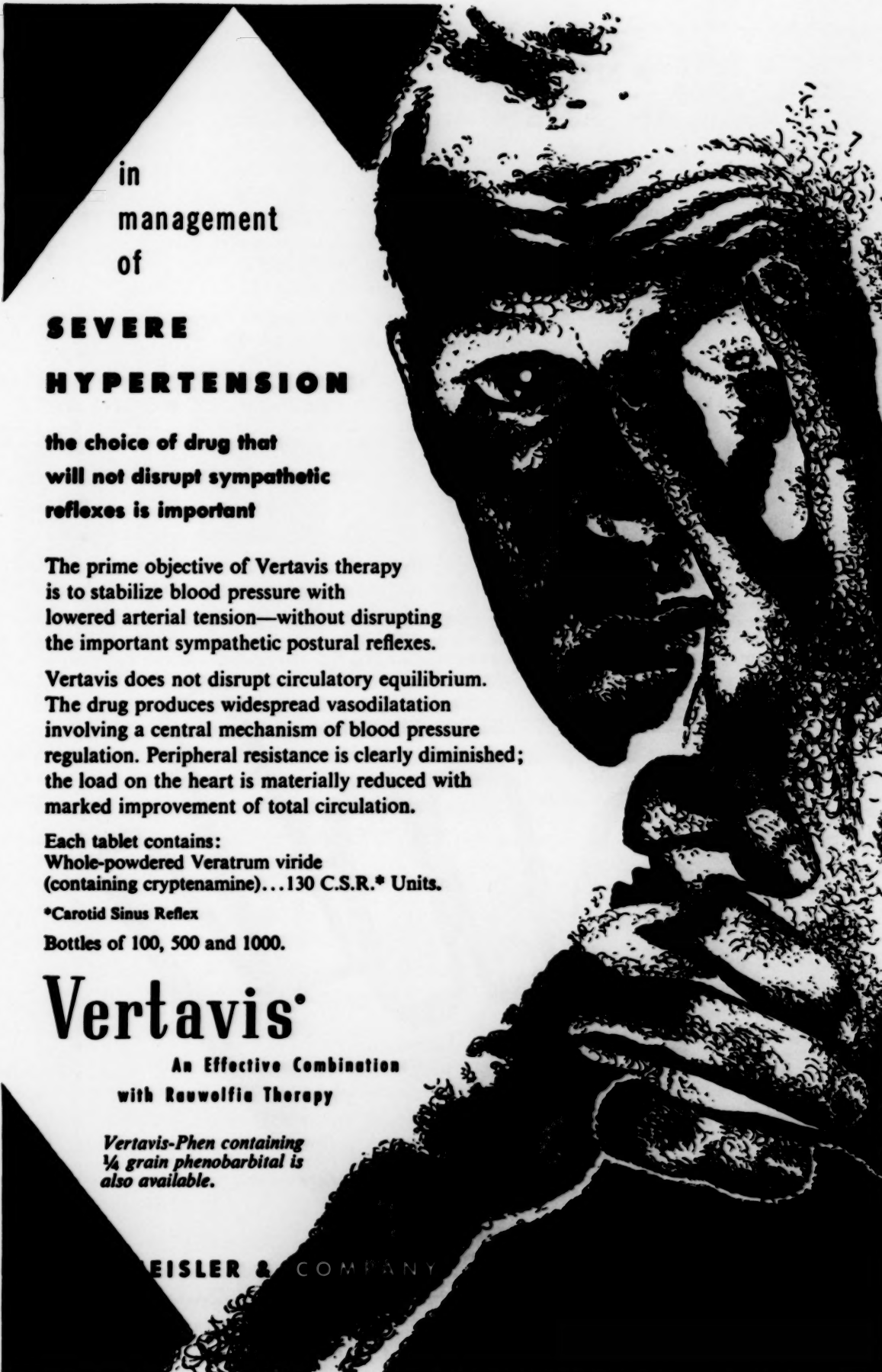
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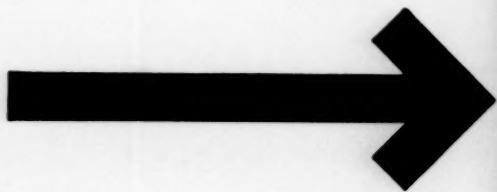
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1. Finnerty, F. A.: Hypertensive Encephalopathy. GP (in Press).

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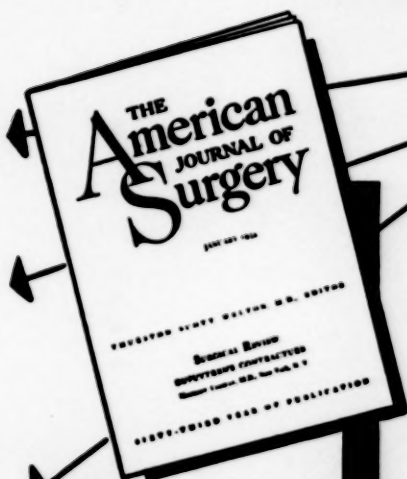
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1. Doyle, P.J., and Livingston, S.: J. Pediat. 43:413 (Oct.) 1953.
2. Forster, F.M.: M. Ann. District of Columbia 23:137 (Mar.) 1954.
3. Lambros, V.S.: Personal Communication.

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